

Editorial

Capacity building for clinical trials in India

Recent events worldwide have challenged the integrity of research on pharmaceutical products and have triggered calls by legislators, medical associations, the International Committee of Medical Journal Editors (ICMJE), the World Health Organization (WHO) and others, for increased accountability and transparency in health products research and development. India, which is projected to have accelerated growth in this sector with the entry of a number of major global and domestic players and a more research focused pharmaceutical industry, is poised to face formidable challenges.

Building the right kind of capacity to meet the anticipated demand for clinical trials in India is an important issue. Along with the optimism for growth in this industry is the concern that vulnerable populations may be exploited. Access to experimental drugs, exposure to latest therapies, improvement in equipment and infrastructure, and creation of new knowledge assets are among the many benefits of this growth. New, difficult to meet expectations and moving local resources away from basic healthcare are among costs and risks of this enterprise. The regulatory regime in India has to identify ways of creating a balance between these benefits and costs/risks.

There is a need at the present time for a strong centralized regulatory regime which can guide high quality development of ethical capacity with extra vigilance but an informed understanding of acceptable risk. Such a system while conforming to international standards needs to be uniquely Indian. It needs to include indigenous medicine, devices, drugs and therapies while incorporating the advent

of biotechnology in general and genomics and proteomics in particular.

While Good Clinical Practices (GCPs) have been clearly spelt out and ethical guidelines have been articulated, our experience with implementation is relatively short. The regulatory system is already stretched in terms of its ability to monitor proper implementation. The expected fast growth in the industry is going to further stretch the capabilities of the system and highlight complexities and unintended consequences.

To address these issues, an interactive workshop on “Building and Managing Clinical Trial Capacity in India : Challenges in Ethics, Equity and Efficiency” was held in Hyderabad in October 2005 by the Indian Council of Medical Research (ICMR), in collaboration with Administrative Staff College of India (ASCI), Hyderabad, and Fordham University of New York. Discussions were held on existing provisions, policy guidelines that need to be developed and the actions to be taken by different stakeholders in the clinical trials industry to make it grow in an efficient and ethical way. Around sixty participants representing a wide cross-section of stakeholders including industry, government, patient advocacy, medical practice, ethics review boards, clinical research organizations (CROs), media and independent investigators discussed issues relating to the conduct of clinical trials in India.

The workshop covered the topics of prioritization of clinical trials, creating a review mechanism for clinical trials, building ethical capacity, building expertise, regulating CROs, clinical trial registries and the role of the media.

Setting clear-cut priorities can help in providing a balance between benefits and risks/costs of the clinical trial enterprise. For the private sector, priorities could mean speedier approvals with a possibility of closer monitoring. It could also mean private public partnership in high priority trials. India should have a system of prioritization based on national interest and patient/subject safety. Clinical trials have different types of risks associated with them. Ability to safely perform a trial is a challenge and should be factored into the prioritization process. Thus, a placebo trial involving vulnerable population (including socio-economically vulnerable) will have a higher risk and may be given a different priority. Higher risk trials need to have special monitoring and more intense review. Risk should include a "site's" ability to safely conduct the trials and the pool from which trial subjects are sought. A number of operational issues to implement such a system of priorities need to be discussed and procedures developed. A working group to measure risk associated with "site capabilities" needs to be constituted. This may be particularly relevant for approval of Phase 1 trials. Criteria for "disallowed" trials as well as guidelines for exceptions should be specified.

Ethics Committees, ethical guidelines and norms, and independent review boards are all different ways of ensuring compliance with established ethical guidelines and good practices. Ethics committees cannot conduct their task responsibly unless they get the data needed to evaluate ethical behaviour. Evaluating conflict of interest, addressing cultural specificities in obtaining informed consent from vulnerable population are some of the critical issues. A subject's ability to independently determine risk and the availability of guaranteed medical care during trials might obscure his/her desire to do a meaningful risk-benefit assessment before providing informed consent. Punitive measures and/or legal liability may help in the implementation of the ethical guideline in trials. Training of ethics committee members, accreditation of these committees and the development of stringent guidelines with detailed operating procedures are necessary.

There is uncoordinated effort in capacity building in clinical trials with little quality control. More regulatory capacity to evaluate NDAs (new drug applications) and more trained principal investigators are needed. There is also a need for more GLP laboratories, a pharmacovigilance programme and the ability to monitor sites for GCP compliance. Mandatory provision of insurance for subjects of trials is another matter that needs to be urgently addressed involving insurance providers with provision for dispute resolution.

There is a need for the urgent development of regulatory capacity in monitoring, oversight, enforcement and approval of trials. An innovative structure with "consultants" may be more feasible. A definition of conflict of interest in the Indian context for these consultants should also be looked into by the working group. The creation of a department of Human Research Subject Protection within Ministry of Health and Family Welfare is also recommended. This needs to be complemented by required legislative changes for the enforcement of such protection. The creation of a public sector CRO for the conduct of need based trials and curriculum changes in medical colleges to teach GCP, ethics, and research methodology will also help in capacity building. A certification for principal investigators is also suggested.

Development of world-class expertise is an outcome of this growth in clinical trials. However, care has to be taken to see that knowledge transfer from abroad and local expertise building takes place in a coordinated fashion. Quality control and joint-trials with reputed global players can give rise to building expertise in this area. Partnerships between public and private sector and with international organizations are a great way to increase expertise. It is recommended that guidelines be provided to ensure that learning does indeed occur through such partnerships. It is also recommended that human resource planning be done carefully to deal with clinical trials of the future (such as molecular diagnostics and molecular epidemiology as well as

latest social science techniques) to ensure that required expertise is available.

There has been an unprecedented growth in CROs in India with most Indian and major multinationals setting up operations in India either directly or as joint ventures. There is no system of registration and/or approval of such organizations. Quality control and potential for abuse remain a major concern for the nation, for which there is need for self regulation through accreditation as well as legislation, to ensure high standards through a system of monitoring by a regulatory agency.

There has been a global demand that all clinical trials be registered as also emphasized by the ICMJE. The ICMJE has made registration of trials mandatory without which they will not publish the results of trials. The WHO has suggested a structure of the registry with a minimum required data set to be followed by all countries. An Indian registry, with the minimum data set and requirements suggested by WHO, needs to be implemented. It is important to include stakeholders from industry, national laboratories and regulatory authority in the development of such a registry in order to get compliance. The help of IT could be used to ensure quality data management.

The media often sensationalize some incidents without adequate investigation. Media on the other hand often complains of lack of transparency on

clinical trials conduct and data. The media plays a critical role in locating abuse of the system especially in identifying unethical trials and unreported serious adverse events (SAEs). The media should also play a responsible role for which some training on clinical trials will help in balanced and in-depth reporting. This should return the fast eroding public trust.

A smart innovative transparent regulatory mechanism including human subject protection is the need of the hour and it is imperative that quick action along the lines suggested should be taken on priority basis as the clinical trial industry is growing very fast in India.

The multi stakeholder interactive workshop at Hyderabad in October 2005 was a good start to initiate discussions amongst the interested parties but much more needs to be done in the near future if the genuine concerns elaborated are to be addressed effectively.

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