New clinical trial rules: Academic trials and tribulations

Academic trials or investigator-initiated studies (IIS) are clinical studies conceived, planned, and managed by individual physician–researchers or an institution or a group of collaborative clinical researchers or institutions.[1,2] IIS include a wide range of studies – clinical trials of new drugs and real-world prospective or retrospective studies. IIS can help physicians in repurposing of drugs and in investigating health research questions relevant to their practice.[1] Data from real-world setting, which are applicable to population studied, can help in developing hospital/state/country-specific health guidelines and policies.[1]

Academic studies are the foundation of a country's clinical research strength. Data from ClinicalTrials.gov show that of 239,401 registered clinical trials between January 1, 2006, and December 31, 2017, 65% were funded by nonindustry academic sources – US National Institutes of Health, US federal agencies, individuals, universities, or organizations – and 35% by industry (Analysis of ClinicalTrials.gov registry December 2018. Data on file). In the US and Europe, 58% and 62% of registered trials, respectively, were funded by academic sources. However, in India, majority – 61% of 3138 registered trials – were industry funded. In contrast, majority of the registered trials from China – 71% of 11,020 trials – were funded by academic sources. The number of registered clinical trials from China (7849) was 6.4 times higher compared to the number from India (1223 trials). Compound annual growth rate (CAGR) of clinical trials from China was (32.1%) 3.8 times higher as compared CAGR of Indian trials (8.5%). It appears that Indian institutions and physicians are not enthusiastic about conducting academic clinical studies. This could be due to several challenges – financial, trained workforce, expertise in research methodology,[1] and time constraints among others. In addition, a new and major challenge since 2014 is regulatory requirements for academic trials. The recently released New Drugs and Clinical Trials Rules 2019 are likely to add to the burden of investigators interested in conducting academic clinical trials.[3]

An academic clinical trial, as per new rules, is a clinical trial initiated by any investigator, academic or research institution for an approved drug for a new indication or new route of administration, or new dose or new dosage form. The results of such a trial are intended solely for academic or research purposes and not for commercial or promotional purpose.[3] Commercial purpose implies the use of the results of academic trial for regulatory approval in India or any country or for use in marketing or promotion of a drug. To comply with these conditions, the investigator, who is responsible as the sponsor, should insist that the legal agreement with the company includes a clause – prohibition of current or future commercial or promotional use of results in India or any country – explicitly. The Ethics Committee (EC), registered with Indian regulatory agency, should confirm that these conditions are included in agreement before the academic trial is approved. Despite having a legal agreement, the question for the EC and the investigator is: How can they ensure that the sponsor doesn't use the results of academic trial for commercial or promotional purpose in any country in future? Under these circumstances, it is unlikely that the industry would be willing to sponsor such academic trials, which do not offer any commercial or promotional benefits. Unless the investigator finds an alternative source of funding – institutional or governmental – such academic trials would be difficult to conduct.

The new rules will also have an impact on other types of academic studies – clinical trials of old drugs or nonintervention observational studies. Such studies will come under the scope of biomedical and health research, which includes studies on basic, applied, and operational research or clinical research, designed primarily to increase scientific knowledge about diseases and conditions (physical or sociobehavioral); their detection and cause; and evolving strategies for health promotion, prevention, or amelioration of disease and rehabilitation but does not include clinical trial as defined in the new rules.[3] The Indian Council of Medical Research (ICMR) 2017 guidelines are applicable to (1) clinical trials of drugs and other interventions; (2) public health research; (3) social and behavioral sciences research for health; (4) human genetic testing and research; (5) biological materials, biobanking, and datasets; and (6) research during humanitarian emergencies and disasters.[4] All such academic research studies will require approval from the Biomedical and Health Research EC registered with the Department of Health Research (DHR).[3]

The new rules mandate that academic clinical trial should be conducted in accordance with ethical principles of ICMR guidelines, and biomedical and health research should be conducted in accordance with ICMR guidelines. These guidelines recommend that while conducting research, the four basic ethical principles such as (a) autonomy, (b) beneficence, (c) nonmaleficence, and (d) justice expanded into 12 general principles should be applied to all biomedical, social, and behavioral sciences research for health involving human participants and their biological material and data.[4] Compliance to these principles – essentiality, voluntariness, nonexploitation, social responsibility, privacy and confidentiality, risk minimization, professional competence, benefit maximization, institutional arrangement, transparency and accountability, totality of responsibility, and environmental protection – would require consideration of several ethical issues during conduct of academic trials.[4] As some of these, for example, EC approval, informed consent process, and special protection for vulnerable population are included in good clinical practice guidelines, a clinical trial investigator undertaking academic trial will be able to comply with them. However, the investigator would wonder how to comply with principle of environmental protection. Does this mean that she should conduct a paperless study? Other ethical issues, for example, ancillary care, postresearch access, benefit sharing, and community engagement would be difficult to handle in the setting of an academic clinical trial. In case academic clinical trial or biomedical and health research proposal has foreign assistance or collaboration, the Health Ministry's Screening Committee approval is a must before initiation.[4] In addition, there are specific recommendations for IIS, especially in the area of institutional oversight and compensation.[4]

As per ICMR guideline, the institution should establish mechanisms to ensure the quality of the data generated and safety of the intervention, such as monitoring, auditing, and Data Safety Monitoring Board. The EC will have a vital role in ensuring compliance to ICMR guidelines by oversight, monitoring, and audit of an academic clinical trial. It is desirable that ICMR guides and trains ECs on how to ensure that academic trial/biomedical health research is conducted in accordance with ICMR ethical principles and guidelines. DHR should also review and audit functioning of registered ECs overseeing academic trials by conducting regular document review or physical audits along the lines of audits conducted by the US Office for Human Research Protections.

The guideline recommends that an investigator/institution should make financial arrangements for the conduct of the study. The study budget should take into consideration requirements for free management and compensation for research-related injury, patient travel/inconvenience, ancillary care, and postresearch access. In research-related harm, the guidelines include not only physical but also psychological, social, legal, or economic harm. Assessment of relationship between injury and research would be expected along the lines of new clinical rules. The amount of compensation would be presumably decided by the EC. But how will the EC assess psychological, social, legal, or economic harm for the purpose of medical management and compensation? There is a need for a detailed guidance from ICMR on the medical management and compensation process for academic trials.

These compensation-related guidelines would result in a big financial burden on the institution. If an academic trial is conducted in 100 high-risk patients, for example, oncology or cardiovascular disease with a high-risk drug, for example, biosimilar, assuming 10%–20% serious adverse events and base compensation amount of Rs. 8 lakhs,[3] total amount to be budgeted would be Rs. 80–160 lakhs. The compensation requirements would deter both the investigator and the institution from initiating academic trials of new drugs. The other option of conducting academic trials with an old marketed drug used as standard treatment is also demanding, as guidelines require that the compensation is applicable to participants in any of the arms of research intervention, control, and standard of care. This compensation requirement is difficult to justify where two marketed standard treatments are compared in a clinical trial or an old drug is used in a repurposing study.

It seems, for an Indian investigator safer approach would be to conduct observational studies on drugs. Even for such studies, the investigator is at a disadvantage. If an investigator initiates an academic observational noninterventional study for new drug surveillance purpose, he/she will have to comply with ICMR guidelines. However, the new rules do not require a sponsor to comply with regulatory provisions and guidelines applicable for clinical trial of a new drug for such studies![3]

Among academic source funded Indian trials registered between 2006 and 2017, only 16% were observational studies. Indian investigators should focus their attention on retrospective observational studies, for example, natural history or health economic issues of common communicable and noncommunicable diseases, which would be less burdensome compared to prospective academic trials and could generate good real-world data, relevant to Indian health-care realities.[5]

In India, only a few leading research institutions have been engaged in academic trials or biomedical and health research. The new clinical rules will make the conduct of academic research arduous for conscientious investigators and increase the burden of ethical compliance for ECs, which are passionate about fulfilling their responsibilities. This may dampen the spirit of institutions and investigators interested in academic clinical research. Academic clinical trials may shift to physicians in private clinics overseen by noninstitutional ECs, which may not be competent in monitoring compliance to new rules and ICMR guidelines. It is desirable that the regulatory authorities and DHR will take pragmatic steps to rationalize the compliance and compensation requirements and to encourage the conduct of innovative academic clinical trials.

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