**Title: Challenges in the governance of biomedical and health research after new drugs and clinical trial rules.**

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**Abstract:**

This review article pertains to the governance of biomedical and health research after the inception of new drugs and clinical trial rules 2019. The present scenario of the functioning of the ethics committee in India and the responsibilities which have been thrust on the ethics committee by the new clinical trial rules are been visualized. The challenges faced by the ethics committee from the inception of the study to its completion has been discussed. Both institutional and independent ethics committees face similar challenges in the review process, but institutional support may be missing for the independent ethics committee. There is a need for rigorous training to all the members involved in the ethics committee functioning and there should be a similar type of supervision by the registration authorities.

**Introduction:**

Ministry of Health and Family Welfare [MoHFW], India, has notified the “New Drugs and Clinical Trials Rules, 2019” on March 2019. The new rules will supersede Part XA and Schedule Y of Drugs and Cosmetics Rules, with immediate effect.New Drugs and Clinical Trials Rules 2019 has defined Biomedical and health research (BHR) defined as research including studies on basic, applied and operational research or clinical research, designed primarily to increase scientific knowledge about diseases and conditions (physical or socio-behavioral); their detection and cause; and evolving strategies for health promotion, prevention, or amelioration of disease and rehabilitation but does not include clinical trial. While Clinical Trial is defined as a new drug or investigational new drug meaning any systematic study of such new drug or investigational new drug in human subjects to generate data for discovering or verifying its clinical or pharmacological including pharmacodynamics, pharmacokinetics or; adverse effects with the objective of determining the safety, efficacy or tolerance of such new drug or investigational new drug (1)

There will be two ethics committees who will cater to these studies:

(i) The Clinical trial, Ethics Committee (CT EC), constituted under rule 7 and registered under rule 8; (Central Drugs Standard Control Organization – CDSCO (Ethics Committee Registration Division) (2)

(ii) Biomedical and health research, Ethics Committee (BHR EC), constituted under rule 16 and registered under rule 17; [Department of Health Research (DHR), Ministry of Health & Family Welfare, Government of India. National Ethics Committee Registry for Biomedical and Health Research (NECRBHR)](https://naitik.gov.in/DHR/Homepage) (3)

Any institution either government or private, hospital either government-affiliated or private who is willing to undertake biomedical and health research should follow the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants 2017. (1) Institutions desirous of conducting biomedical and health research as well as clinical trials or bioavailability or bioequivalence study shall require obtaining registration from specified authorities as provided in rule 8 and rule 17. In India, we have an institutional ethics committee and independent ethics committees, both have the same mandate of ethics governance. For registration of institutional as well as for independent ethics committee, a checklist is provided at the DHR website and in new CT rules (Third schedule – Table 1). Both have the same documentation list. CDSCO is doing re-registration of the ethics committee (EC) and is giving approval for 5 years, while DHR is providing only provisional registration for 2 years. But in the meantime, they will scrutinize the documents and issue final registration for 5 years. If not satisfied with the applicant, DHR can reject the application by giving reasons. The applicant can appeal to the Central Government in the Ministry of Health and Family Welfare. The government may, after enquiry, as deemed necessary, and after giving an opportunity of being heard, will pass an order within 45 working days. The ECs registered with DHR are required to make an application for renewal of registration at least ninety days prior to the date of the expiry of its final registration. In case there is a change in the composition of registered EC in an institution, it should be reported to the concerned authority. The EC who will fail to comply with any provision mentioned in rule 17, the authority designated under sub-rule (1), may, after giving an opportunity to show cause and after offering an opportunity of being heard may either issue warning to the EC describing the deficiency or suspend or cancel the registration issued or debar its members to oversee any biomedical health research in future for such period as may be considered appropriate.The relevant annexures to biomedical research are summarized in Table 1. (3)

Table 1. Relevant annexures to biomedical research

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| Third schedule, Table 1 | Information to be submitted by an applicant for the grant of registration of EC and format for according approval |
| Third schedule, Table 6 | Structure, content, and format for the clinical trial report |
| Eighth schedule,  Form CT-01 | Application for registration/renewal of EC relating to clinical trial or bioavailability and bioequivalence study or biomedical health research |
| Eighth schedule,  Form CT-03 | Grant of registration of EC relating to biomedical health Research |

At present 1163 ECs are re-registered on the CDSCO website, in which Institutional EC are 1047 and independent EC are 116. While registration on the DHR website has just started in September 2019. (1,3)

**Ethics committee - role and responsibility:**

EC reviews projects based on the three basic ethical principles for research involving human subjects: respect for persons, beneficence, and justice. (4) The type of studies reviewed by BHR EC would be pertaining to modern medicine, traditional systems of medicine, device, diagnostic trials, questionnaire-based studies, data analysis from either public domain or from internal department database or institution documents, leftover sample research, community research, surgical inventions and death certificate analysis. Many non-drug studies are also submitted such as social research, public health research, preventive research, and cost analysis. According to the Indian Council of Medical Research (ICMR) guidelines, the type of EC review (full board review, expedited and exempt from review) is based on the risk involved in the research. The risk is categorized into less than minimal risk, minimal risk, a minor increase over minimal risk or low risk and more than minimal risk or high risk. The probable designs of the studies reviewed by EC are prospective observational, cross-sectional, cohort, interventional, retrospective, retro-prospective. The EC reviews protocol and comments are sent on regulatory, administrative, scientific and on ethical grounds.

**The challenges usually faced by the ethics committee**

1. **Before approval of the study** –

New Drugs & Clinical Trials Rules 2019 have defined the composition of EC as per ICMR guideline 2017.

* It mentions that 50% of the members should be non-affiliated and the number of members in an EC should preferably be between 7 and 15 and a minimum of five members should be present to meet the quorum requirements. (4) So, this regulation is a good move for unbiased decision making by EC if the decision goes for voting or consensus also. But it is a difficult task for EC functioning in the place with a single medical college to get non-affiliated members. In case, where non**-** affiliated members are not available in the same city, they must travel from another city to attend the meeting. So, the travel allowance for such members would be definitely more as compared to the in city members.
* Policy regarding training for new and existing committee members along with standard operating procedures (SOP) has been made mandatory. If the member is found to be untrained or training documents are missing, then the member is disqualified from the post of member of the EC. (1) This rule was initially not compulsorily followed , but now before appointing new members , you have to recruit trained members or give them training .This will probable enhance the EC review process and will bring uniformity across ECs in India.
* The EC should maintain documents related to clinical study for a period of five years after completion of such clinical study. (1) The ECs always had issues with limited space , now they need space for archival as per law .

**Solution:** Institution should provide staff, equipment, and funding for smooth EC functioning (ongoing arrangement for training EC members, travel allowance for non-affiliated members). Along with that, the institution should support by providing space for office, for conducting meeting and for archiving of the documents.

The investigator in investigator-initiated studies also have the responsibility of the sponsor, so the investigator should take responsibility for research in totality. In a prospective interventional study, if the risk is more than a minimal or minor increase over minimal risk; the financial coverage for compensation for participation as well as the study-related injury is an issue. Principal investigator (PI) must make budgetary arrangements for the conduct of the study which includes participant investigations, his/her work up and intervention related treatment. PI must also provide insurance or give an undertaking that he/she is ready to pay compensation if any serious adverse event (SAE) occurs and is related to the trial. But in many cases, such provisions are not made. As per ICMR guidelines, it is also the responsibility of the host institution to provide compensation or cover for insurance for research-related injury and harms. (4) But, such arrangements are missing from the host institution. So, many times EC takes decision-based on the undertaking given by the PI, without any financial arrangement in place. This decision again can vary with different studies. The decision can be not allowing such studies, or few EC may allow. But if something goes wrong in such research, EC also can face the brunt of legal action.

**Solutions:** Investigators should write for research grants to funding agencies. The institution should have a corpus fund for managing this situation. They can seek advice from many such research-oriented institutes who have such arrangements in place. EC should also safeguard its interest by indemnifying for each such study.

In collaborative research for drug or diagnostic trials, the collaborator might give only drug-free of cost or pay only for investigations or take a sample of some unwanted tissue for doing secondary research or store tissue for many years or create products from it. The memorandum of understanding (MoU) between the collaborative institutes or individuals doing such research should have clear objectives as to why they are collaborators and in the process is there any violation of patient rights, investigator rights or institutional rights. Informed Consent Document also does not clarify the role of collaborators. ECs have a tough job of finding the details of these sponsors. They range from individuals, sponsor companies, NGOs to specialty trusts. The intensions are not very clearly mentioned in the MoU. EC has to take decisions by being vigilant. Only trained and experienced EC can take the right decision in such cases.

Government-funded studies are usually observational and multicentric, they provide with MoU consisting of the log of delegation, free management of treatment which is provided by the concerned institutes. But payment for participation or compensation for study-related injury is not mentioned. They behave like funders but do not take responsibility of the sponsor. In such cases, EC faces a big challenge approving such protocol. Even if there is no clarity for coverage of compensation in interventional studies, EC tends to be biased for such studies and approve such studies. Now the stand of EC may be different or it will take the regulation in consideration while decision making .

In traditional systems of medicine research, usually, insurance is not provided by company doing research on marketed product. Although, MoU mentions the log of delegation with the role and responsibilities of all collaborators and managing free patient care; many times risk is not defined as they are multi-ingredient products or there is no adequate literature available. So, reviewing and approving such studies is also a challenging task for EC.

The protocol of intervention study submitted by investigators are incomplete. The area where protocols are usually incomplete is in rationale, study design, description of the methodology, sample size and statistical tests. The investigator never defines harm in the protocol, nor does a risk-benefit analysis. The vulnerable population needs special protection, but vulnerable population and vulnerability is usually not defined in the protocol. The possible reason for this is the inadequate training of the investigators for conducting research. These untrained researchers may be resident doctors doing research for the first time as their dissertation. In KEM Hospital, Mumbai there are 340 PI in 43 different departments and only 10 sites have a site-specific SOP. These are the sites that are doing regulatory studies. Training of PI along with student investigators is the biggest challenge. The workload of EC increases because the review process has to be extensive in these cases. If the documentation is weak, EC would ask too many queries and there is a delay in the approval process. Some investigators are not able to answer the queries and they just quit or don’t reply to the queries because they are untrained to answer them. (5) Also, if the EC members are untrained, approval can happen without proper ethics review.

**Solutions:** Institution must make arrangements for regular training for investigators through the research methodology workshop. EC member training should be case-based, it should be member specific (e.g. a legal person should be trained to review documents related to Clinical trial agreement (CTA), MoU, insurance, regulatory approval). EC staff should be trained in administration as well as in ethics. EC SOP should define the vulnerable population and vulnerability . There should be a checklist for the investigator and reviewer for identification and providing protection to such population or it can be case-specific. Training of EC members in reviewing protocols and updating them with the latest ICMR guidelines and new CT rules. There should be guidance created for investigators in AE reporting, PD reporting, payment for participation, vulnerable population /vulnerability and site-specific SOPs. Government should make provisions for payment for participation as well for compensation for study related injury for more than minimal risk protocol while approval.

1. **During the conduct of the study**:

Mechanisms to ensure the quality of the data generated and safety of the intervention is usually done by passive monitoring by the majority of the ECs, where the investigators submit annual updates and safety updates reports. The only deviations found by EC in annual updates is the deviation in sample size (e.g. approved sample size is 60 and investigator has recruited 100). The challenging part is annual updates are not submitted by PI unless reminded. Many times, EC forgets to send reminders or follow up studies, so EC also deviates its own standard operating procedures (SOPs). Annual reports which are submitted are also incomplete. The incompleteness of the annual update is seen in the following areas. They do not mention the number of participants approved, the number of participants screened, and the number of participants active versus completed, if withdrawn its reasons. There are a lot of deviations in annual reporting itself, where if participants are recruited in this period, they are not under EC oversight. Taking actions for such PI becomes a task. Protocol deviations (6), adverse events, SAE (7) are not reported by the investigators in academic studies . Based on the data provided by the PI, EC has to take the decision whether to allow the study to continue or discontinue based on the risk-benefit analysis. So, as this data is incomplete, taking decisions for EC is challenging.

**Solutions:** Active monitoring as suggested by ICMR 2017 can find lapses in study conduct. This auditing can be done by the internal Data and Safety Monitoring Board (DSMB). Very few institutes have internal DSMB which monitors all the studies e.g.; TATA Hospital has a DSMB as a sub-committee. (8) Otherwise, EC has to monitor all the studies. The institution should create an ethics/research department as a separate department and members should give dedicated time for this activity (for initial to continued review, monitoring of studies and part of SAE sub-committee). The institution must allocate budget for training DSMB members and for site monitoring.

**3.After completion of the study:**

Investigators do not submit study completion reports even after multiple reminders by EC. So, the archival does not start unless the completion report is submitted, thus the study file remains active in EC office for a long time. This is a challenge to EC to maintain such files when inadequate space is available for the EC office. Many times, investigators submit publication in place of completion report and EC tends to find deviations in sample size or studies getting published before EC approval.

**Solutions: I**nvestigators must be trained to submit a completion report on time. EC can send warning letters or can punish such investigators (who have such deviations) by not reviewing their protocol for six months.

Independent EC has also been allowed to review academic studies done in private clinics or institutions not having EC. So, they will face similar challenges in the review process as institutional EC. As there is no institutional support their challenges for funding may be different from institutional EC.

**Conclusion:**  
New drugs & clinical trial rules have made EC powerful and responsible for protecting the rights,well-being and safety of the participants. But are ECs equipped to take such responsibility without any institutional support and regular supervision by registration authorities

**References:**

1. Ministry of Health and Family Welfare. Govt of India. Notification. The Gazette of India: Extraordinary, Part II, Section 3, Subsection (i), New Delhi, March 2019 [Internet]. [cited 2019 Nov 1]. p. 1–264. Available from: https://cdsco.gov.in/opencms/export/sites/CDSCO\_WEB/Pdf-documents/NewDrugs\_CTRules\_2019.pdf

2. Central Drugs Standard Control Organization: Ethics Committee Re-Registration [Internet]. [cited 2019 Nov 1]. Available from: https://cdsco.gov.in/opencms/opencms/en/Clinical-Trial/Ethics-Committee/Ethics-Committee-Re-Registration/

3. Department of Health Research, Ministry of Health & Family Welfare, Government of India. National Ethics Committee Registry for Biomedical and Health Research (NECRBHR) [Internet]. [cited 2019 Nov 1]. Available from: https://naitik.gov.in/DHR/Homepage

4. Indian Council of Medical Research. National ethical guidelines for biomedical and health research involving human participants. New Delhi: Indian Council of Medical Research; 2017. [Internet]. 2017 [cited 2018 Apr 20]. Available from: http://www.icmr.nic.in/guidelines/ICMR\_Ethical\_Guidelines\_2017.pdf

5. Kuyare SS, Marathe PA, Shetty YC, Kamat SK, Katkar J V, Thatte UM. Projects not initiated by investigators: a retrospective analysis of the queries raised by the institutional ethics committees of a teaching hospital. J Postgrad Med. 60(1):46–50.

6. Jalgaonkar S V, Bhide SS, Tripathi RK, Shetty YC, Marathe PA, Katkar J, et al. An Audit of Protocol Deviations Submitted to an Institutional Ethics Committee of a Tertiary Care Hospital. PLoS One. 2016;11(1):e0146334.

7. Tripathi RK, Marathe PA, Kapse S V, Shetty YC, Kamat SK, Thatte UM. Serious Adverse Events Reports: Analysis and Outcome of Review by an Institutional Ethics Committee of a Tertiary Care Hospital in Mumbai, India. J Empir Res Hum Res Ethics. 2016;11(3):267–73.

8. Tata Memorial Centre Data and Safety Monitoring Sub Committee Policy and Procedures Manual [Internet]. 2003 [cited 2019 Nov 2]. Available from: https://tmc.gov.in/research/DSMSC SOPs.pdf