New Drugs and Clinical Trials Rules 2019: Changes in responsibilities of the ethics committee

Neelu Singh, Nivedita J. Madkaikar[1], Partha M. Gokhale[2], Deven V. Parmar[3]

Department of Clinical Research, Zydus Research Centre, Cadila Healthcare Limited, Ahmedabad, Gujarat, [1]Department of Clinical Development, Abbott Healthcare Private Limited, [2]Department of Medical, Boehringer Ingelheim India Private Limited, Mumbai, Maharashtra, [3]Department of Clinical research and Development, Clinical R and D, Zydus Discovery DMCC, Dubai, UAE

Abstract

The New drugs and Clinical trials rules 2019 (New rules) was introduced on 19th March 2019 by Government of India. New rules have set specific requirements for ethics committee (EC). The EC is required to follow requirements set as per New rules and to forward their report to Central Licensing Authority (CLA). This document is divided into different sections like definitions and applicable chapter & schedules for EC; changes related to registration of clinical studies and biomedical and health research; changes related to constitution, functions, proceedings, responsibility of EC for clinical trial; maintenance of records by EC; suspension and cancellation of registration of EC, post-trial access of drugs, changes and clarity related to academic clinical trials and role of ECs in compensation and medical management process.

Keywords: Central licensing authority, ethics committee, new rules

Address for correspondence: Mrs. Neelu Singh, Department of Clinical Research, Zydus Research Centre, Cadila Healthcare Limited, Survey No. 396/403, Sarkhej-Bavla, N. H. No. 8A, Moraiya, Ahmedabad - 382 213, Gujarat, India.
E-mail: neelu.singh@zyduscadila.com
Received: 18-12-19, **Accepted:** 18-12-19, **Published:** 31-01-20.

INTRODUCTION

This document summarizes major changes affecting ethics committee (EC) after coming into force of the New Drugs and Clinical Trials Rules 2019 (New rules), i.e. GSR 227 (E) by India's Ministry of Health and Family Welfare (MoHFW).

DEFINITIONS, APPLICABLE CHAPTERS, AND SCHEDULES FOR ETHICS COMMITTEE

EC means, for the purpose of:

i. Clinical trial (CT), EC, constituted under Rule 7 and registered under Rule 8 of the New CT rules
ii. Biomedical and health research, EC, constituted under Rule 16 and registered under Rule 17 of the New CT rules.

There are two chapters which are dedicated to EC. The new rules have separated the ethical governance system by having two different types of ECs with two authorities for their registration and monitoring.

Chapter	Topic
Chapter III	EC for CT, bioavailability (BA), and bioequivalence (BE) study
Chapter IV	EC for biomedical and health research

EC = Ethics committee

Access this article online	
Quick Response Code:	Website: www.picronline.org
	DOI: 10.4103/picr.PICR_208_19

How to cite this article: Singh N, Madkaikar NJ, Gokhale PM, Parmar DV. New drugs and clinical trials rules 2019: Changes in responsibilities of the ethics committee. Perspect Clin Res 2020;11:37-43.

There are three schedules which are to be referred for EC functioning:

Schedule	Topics
Third schedule	Conduct of CT
Seventh schedule	Formula to determine the quantum of compensation in the cases of CT-related injury or death
Eighth schedule	Forms for application and issuance of permissions

REGISTRATION OF THE ETHICS COMMITTEE

Every EC shall be required to register with the authority designated by the Central Government in the MoHFW, Department of Health Research (DHR), under these rules for which an application shall be made in Form CT-01 to the Central Licensing Authority (CLA).

Every EC shall furnish information and documents as specified in Table 1 of the third schedule along with the application made in Form CT-01.

Grant and validity of ethics committee registration certificate

The CLA shall grant registration to EC in Form CT-02 after being satisfied with the compliance of these rules. This registration certificate is valid for a period of 5 years from the date of its issue, unless suspended or cancelled by the CLA.

Rejection of ethics committee registration certificate

If the CLA is not satisfied with the compliance of these rules by the applicant EC, it may reject the application, for reasons to be recorded in writing, within a period of 45 working days, from the date of the receipt of the application made in Form CT-01. After rejection, the applicant EC may file an appeal before the Central Government in the MoHFW within 60 working days from the date of the receipt of order of such rejection. The Central Government may after such inquiry and after giving an opportunity of being heard to the appellant shall dispose of the appeal within a period of 60 working days from the date on which the appeal has been filed.

Table 1: List of documents

Name of document
Constitution and composition of the EC
Curriculum vitae of all members of the EC
SOPs of EC
National and international guidelines followed by the EC
Copies of the protocol, data collection formats, case report forms, investigators' brochures, etc., submitted for review
All correspondence with committee members and investigators regarding application, decision, and follow-up
Agenda of all EC meetings and minutes of all EC meetings with signature of the chairperson
Copies of decisions communicated to applicants
Records relating to any order issued for premature termination of study with a summary of the reasons thereof
Final report of the study including microfilms, compact disks, or video recordings
Recommendation given by EC for determination of compensation
Records relating to the SAE, medical management of trial subjects, and compensation paid

EC=Ethics committee, SOPs=Standard operating procedures, SAE=Serious adverse event

Renewal of registration of ethics committee for clinical trial

EC may make an application for renewal of registration in Form CT-01 along with documents as per Table 1 of the Third Schedule 90 days prior to the date of the expiry of the registration. If the application for renewal of registration is received by the CLA 90 days prior to the date of expiry, the registration shall continue to be in force until an order is passed by the CLA. The CLA shall scrutinize the information as per the application and can renew the registration if all requirements of these rules have been complied.

A fresh set of documents shall not be required to be furnished, if there are no changes in such documents furnished at the time of grant of registration and the applicant renders a certificate to that effect indicating that there is no change.

If there is any noncompliance of these new rules, then the CLA can also reject the application for renewal of registration of the EC for CT, for reasons to be recorded in writing, within a period of 45 working days from the date of renewal application is made.

Registration of the ethics committee relating to biomedical and health research

Any institution or organization, which intends to conduct biomedical and health research, shall be required to have an EC to review and oversee the conduct of such research as detailed in the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants.

Such EC shall be required to register with the authority designated by the Central Government in the MoHFW, DHR, through DHR online portal with domain name: https://naitik.gov. in/DHR/Homepage.

The National Ethic Committee Registry for Biomedical and Health Research has been put in place within the DHR to facilitate the receipt and processing of application seeking registration and to assist the authority in the discharge of duties.

A provisional registration certificate shall remain valid for a period of 2 years and final registration granted in Form CT-03 shall remain valid for 5 years from the date of its issue.

The function, proceedings of EC, and maintenance of records shall be as per the Indian Council of Medical Research (ICMR) guideline involving human participants.

CONSTITUTION OF THE ETHICS COMMITTEE FOR CLINICAL TRIAL

a. EC shall have a minimum of seven members from medical, nonmedical, scientific, and nonscientific areas with at least
    i. One lay person
    ii. One woman member
    iii. One legal expert
    iv. One independent member from any other related field such as social scientist or representative of nongovernmental voluntary agency or philosopher or ethicist or theologian.

b. At least 50% of its members who are not affiliated with the institute or organization in which such committee is constituted
c. The chairperson should not be affiliated with the institute or organization and shall be appointed by such institute or organization
d. The member secretary should be affiliated with the institute or organization and shall be appointed as by such institute or organization
e. At least one member whose primary area of interest or specialization is nonscientific and at least one member who is independent of the institution
f. The members representing medical scientists (preferably pharmacologist) and clinicians shall possess at least postgraduate qualification in their respective area of specialization, adequate experience in their respective fields, and requisite knowledge and clarity about their role and responsibility as committee members
g. Every member shall undergo training and development programs as may be specified by the CLA from time to time. Provided that any member who has not successfully completed shall be disqualified to hold the post of member of the EC and shall cease to be a member of such committee

EC should have training procedure at defined frequency or as per requirement as defined in EC standard operating procedure (SOP). All training records of EC members should be available with EC for future audits and inspection activities.

h. As far as possible, based on the requirement of research area such as human immunodeficiency virus or genetic disorder, specific patient group may also be represented in EC
i. No member of an EC, having a conflict of interest, shall be involved in the oversight of the CT or BA/BE study protocol being reviewed by it, and all members shall sign a declaration to the effect that there is no conflict of interest
j. While considering an application which involves a conflict of interest of any member of the EC, such member may voluntarily withdraw from the EC review meeting, by expressing the same in writing to the chairperson. Details in respect of the conflict of interest of the member shall be duly recorded in the minutes of the meetings of the EC
k. All the members of the EC shall follow the provisions of these rules, Good Clinical Practices Guidelines, and other regulatory requirements to safeguard the rights, safety, and well-being of trial subjects.

FUNCTIONS OF ETHICS COMMITTEE

a. EC shall review and accord approval to a CT, BA/BE study protocol, and other related documents and oversee the conduct of CT to safeguard the rights, safety, and well-being of trial subjects in accordance with these rules, Good Clinical Practices Guidelines, and other applicable regulations
b. EC shall make, at appropriate intervals, an ongoing review of the CTs for which it has accorded approval which may be based on
    i. Periodic study progress reports furnished by the investigators or
    ii. Monitoring and internal audit reports furnished by the sponsor or
    iii. By visiting the study sites.

c. Indicate the reasons while rejecting or asking for a change or notification in the protocol in writing, and a copy of such reasons shall also be made available to the CLA
d. The EC shall analyze all documents pertaining to serious adverse event (SAE) of any subject during any CT or BA/BE study and shall forward the SAE report to CLA as per requirement
e. At any stage of the CT, EC may order discontinuation or suspension of the CT if it comes to a conclusion that the trial is likely to compromise the right, safety, or well-being of the trial subject and the same shall be intimated to the head of the institution conducting CT and the CLA

f. EC shall allow any officer authorized by the CLA to enter with or without prior notice to inspect the premises, any record, or any documents related to CT; furnish information to any query raised by such authorized person, in relation to the conduct of CT; and to verify compliance with the requirements of these rules and other relevant regulations
g. EC shall comply with the requirements or conditions in addition to the requirements specified under the Act and these rules may be specified by the CLA with the approval of the Central Government, to safeguard the rights of CT subject or BA/BE subject.

PROCEEDINGS OF ETHICS COMMITTEE FOR CLINICAL TRIAL

a. Quorum requirement:

All protocol and related documents shall be reviewed by at least five of its EC members as:

i. Medical scientist (preferably a pharmacologist)
ii. Clinician
iii. Legal expert
iv. Social scientist or representative of a nongovernmental voluntary agency or a philosopher or an ethicist or a theologian or a similar person
v. Lay person.

b. Constitution of subcommittees: EC may constitute one or more subcommittees of its members to assist in the functions assigned to it
c. Association of experts: EC may associate such experts who are not its members, in its deliberations, but such experts shall not have voting rights
d. Change in membership: Any change in the membership or the constitution of the registered EC shall be intimated in writing to the CLA within 30 working days
e. EC should update their EC membership as per the New Drugs and Clinical Trials Rules as soon as possible and intimate CLA about this change in membership within 30 working days.

MAINTENANCE OF RECORDS

EC shall maintain data for a period of 5 years after completion of such CT or BA/BE study [Table 1].

SUSPENSION OR CANCELLATION OF REGISTRATION OF ETHICS COMMITTEE

a. If CLA is of the opinion that any EC fails to comply with any provision of the Act or these rules, it may issue a show cause notice to such EC specifying therein such noncompliances and the period within which reply shall be furnished by such EC
b. On receipt of reply for the show cause notice within a period specified in the show cause notice, the CLA may give an opportunity of being heard, in person to such EC
c. After consideration of the facts and reply given by the EC, the CLA may take one or more of the following actions, namely:
   i. Withdraw the show cause notice issued
   ii. Issue warning to the EC describing the deficiency or defect observed during inspection or otherwise, which may adversely affect the rights or well-being of the trial subject or the validity of CT or BA/BE study
   iii. Reject the results of CT or BA/BE study
   iv. Suspend for such period as considered appropriate or cancel the registration issued under Rule 8
   v. Debar its members to oversee any CT in future for such period as may be considered appropriate.

d. EC member may file an appeal within a period of 60 working days of the receipt of the order and the Central Government may, after inquiry, and after giving an opportunity of being heard, pass such order in relation thereto as it thinks appropriate in the facts and circumstances of the case within a period of 60 working days from the date of filing of the appeal.

RESPONSIBILITY OF ETHICS COMMITTEE

a. EC is responsible to safeguard the rights, safety, and well-being of all trial subjects of reviewed and approved study/trial protocol
b. The EC should exercise particular care to protect the rights, safety, and well-being of all vulnerable subjects participating in the study, for example, members of a group with hierarchical structure (e.g. prisoners, armed forces personnel, and staff and students of medical, nursing, and pharmacy academic institutions), patients with incurable diseases, unemployed or impoverished persons, patients in emergency situation, ethnic minority groups, homeless persons, nomads, refugees, minors, or other incapable of personally giving consent
c. EC should have documented SOPs and should maintain a record of its proceedings
d. EC should make, at appropriate intervals, an ongoing review of the trials for which they have reviewed the protocol. Such a review may be based on the periodic study progress reports furnished by the investigators or monitoring and internal audit reports furnished by the sponsor or visiting the study sites

e. In case an EC revokes its approval accorded to a trial protocol, it must record the reasons for doing so and at once communicate such a decision to the investigator as well as to the CLA.

POSTTRIAL ACCESS OF DRUGS

If any investigator of a CT of investigational new drug or new drug has recommended posttrial access of the said drug after completion of CT to any trial subject and the same has been approved by the EC for CT, the posttrial access shall be provided by the sponsor of such CT to the trial subject free of cost in special circumstances as follows:

i. If the CT is being conducted for an indication for which no alternative therapy is available and the investigational new drug or new drug has been found to be beneficial to the trial subject by the investigator and
ii. The trial subject or legal heir of such subject, as the case may be, has consented in writing to use posttrial investigational new drug or new drug, and the investigator has certified and the trial subject or his/her legal heir, as the case may be, has declared in writing that the sponsor shall have no liability for posttrial use of investigational new drug or new drug.

ACADEMIC CLINICAL TRIAL PROCESS

Academic CT means a CT of a drug already approved for a certain claim and initiated by any investigator and academic or research institution for a new indication or new route of administration or new dose or new dosage form, where the results of such a trial are intended to be used only for academic or research purposes and not for seeking approval of the CLA or regulatory authority of any country for marketing or commercial purpose.

a. No permission for conducting an academic CT shall be required for any drug from the CLA where
    i. The CT in respect of the permitted drug formulation is intended solely for academic research purposes for a new indication or new route of administration or new dose or new dosage form and
    ii. The CT referred to in clause (i) has been initiated after prior approval by the EC for CT and
    iii. The observations generated from such CT are not required to be submitted to the CLA and
    iv. The observations of such CT are not used for promotional purposes.
b. In the event of a possible overlap between the academic CT and CT or a doubt on the nature of study, the EC concerned shall inform the CLA in writing indicating its views within 30 working days from the date of receipt of application to that effect
c. CLA shall examine it and issue necessary clarification, in writing, within 30 working days from the date of receipt of communication from the EC. If the CLA does not send the required communication to such EC within 30 working days from the date of receipt of communication from the said EC, it shall be presumed that no permission from the CLA is required
d. The approved academic CT shall be conducted in accordance with the approved CT protocol and ethical principles specified in the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, notified by the ICMR with a view to ensuring protection of rights, safety, and well-being of trial subject during conduct of CT of licensed and approved drug or drug formulation for any new indication or new route of administration or new dose or new dosage form for academic research purposes.

COMPENSATION AND MEDICAL MANAGEMENT PROCESS

a. Compensation in case of injury or death in CT or BA/BE study of new drug or investigational new drug will be given as follows:
    i. In case of death of the trial subject, the legal heir of the trial subject shall be provided financial compensation by the sponsor or its representative in accordance with Rule 42 of the New CT rules, 2019. The financial compensation shall be in addition to any expenses incurred on the medical management of the trial subject
    ii. In case of any permanent disability or any other injury, the trial subject shall be provided financial compensation by the sponsor or its representative in accordance with Rule 42. The financial compensation shall be in addition to any expenses incurred on the medical management of the trial subject
    iii. In the event of an injury, not being permanent in nature, the quantum of compensation shall be commensurate with the loss of wages of the subject as provided in the Seventh Schedule
    iv. The sponsor or its representative shall give an undertaking along with the application for CT permission to the CLA to provide compensation in the case of CT-related injury or death for which subjects are entitled to compensation
    v. If the sponsor or its representative, who has obtained permission to conduct study, fails to provide financial compensation, then the CLA

shall, after affording an opportunity of being heard, by an order in writing, suspend or cancel the CT or BA/BE study or restrict the sponsor including its representative, who has obtained permission to conduct CT or BA/BE study, to conduct any further CT or BA/BE study or take any other action for such period as considered appropriate in light of the facts and circumstances of the case.

b. Management in CT or BA/BE study of new drug or investigational new drug

In case of injury to any subject during the study, the sponsor shall provide free medical management to such subject as long as required as per the opinion of the investigator or till such time it is established that the injury is not related to the CT or BA/BE study, as the case may be, whichever is earlier.

c. Consideration of injury or death or permanent disability to be related to CT or BA/BE study.

Any injury or death or permanent disability of a trial subject occurring during CT or BA/BE study due to any of the following reasons shall be considered as CT or BA/BE study-related injury or death or permanent disability, namely:

i. Adverse effect of the investigational product
ii. Violation of the approved protocol, scientific misconduct, or negligence by the sponsor or his/her representative or the investigator leading to SAE
iii. Failure of investigational product to provide intended therapeutic effect where the required standard care or rescue medication, though available, was not provided to the subject as per CT protocol
iv. Not providing the required standard care, though available to the subject as per CT protocol in the placebo-controlled trial
v. Adverse effects due to concomitant medication excluding standard care, necessitated as part of the approved protocol
vi. Adverse effect on a child *in utero* because of the participation of the parent in the CT
vii. Any CT procedures involved in the study leading to SAE.

SERIOUS ADVERSE EVENTS REPORTING, COMPENSATION, AND MEDICAL MANAGEMENT PROCESS

The investigator shall report all SAEs to the CLA, the sponsor or its representative, and the EC within 24 h of their occurrence, and if the investigator fails to report any SAE within the stipulated period, then he/she shall have to furnish the reasons for delay to the satisfaction of the CLA along with the report of the SAE.

a. Case of SAE of death shall be examined in the following manner, namely:
   i. The sponsor or its representative and the investigator shall forward their reports on SAE of death after due analysis to the CLA and the head of the institution within 14 days of the knowledge of occurrence of SAE of death
   ii. The EC for CT shall forward its report on SAE of death after due analysis along with its opinion on the financial compensation, if any, determined in accordance with the formula specified in the Seventh Schedule, to be paid by the said sponsor or its representative, to the CLA within a period of 30 days of receiving the report of the SAE of death from the investigator
   iii. The CLA shall constitute an independent expert committee to examine the cases and make its recommendations to the said authority for arriving at the cause of death and quantum of compensation in case of CT-related death. All reports as received from the investigator, sponsor, or its representative and the EC shall be forwarded by the CLA to the chairperson of the expert committee for examination
   iv. The expert committee shall examine the report of SAE of death and make its recommendations available to the CLA for the purpose of arriving at the cause of the SAE of death within 60 days from the receipt of the report of the SAE, and the expert committee while examining the event may take into consideration the reports of the investigator, sponsor, or its representative and the EC for CT
   v. The expert committee shall also recommend the quantum of compensation as per the specified formula to be paid by the sponsor or his/her representative in case of study-related SAE of death
   vi. The CLA shall consider the recommendations of the expert committee and shall determine the cause of death with regard to the relatedness of the death to the CT or the BA/BE study, as the case may be
   vii. In case of CT or BA/BE study-related death, the CLA shall, after considering the recommendations of the expert committee, by order, decide the quantum of compensation, determined as per the

formula specified in the Seventh Schedule, to be paid by the sponsor or its representative and shall pass orders as deemed necessary within 90 days of the receipt of the report of the SAE

viii. The sponsor or its representative shall pay the compensation in case the SAE is related to CT or the BA/BE study, within 30 days of the receipt of such order.

b. A case of SAE other than death, i.e. cases of SAEs of permanent disability or any other injury, shall be examined in the following manner, namely:
   i. The sponsor or its representative and the investigator shall forward their reports on SAE after due analysis to the CLA, chairperson of the EC, and the head of the institution within 14 days of the reporting of SAE
   ii. The EC shall forward its report on SAE of other than deaths, as the case may be, after due analysis along with its opinion on the financial compensation, if any, determined in accordance with the formula specified in the Seventh Schedule, to be paid by the sponsor or its representative within 30 days of receiving the report of the SAE
   iii. The CLA shall determine the cause of the injury and pass order or may constitute an independent expert committee, wherever it considers necessary, to examine such SAE, and such independent expert committee shall recommend to the CLA for the purpose to arrive at the cause of the SAE and also the quantum of compensation within a period of 60 days of the receipt of the report of the SAE
   iv. In case of CT or BA/BE study-related injury, the CLA shall, by order, decide the quantum of compensation, determined in accordance with the formula specified in the Seventh Schedule, to be paid by the sponsor or his/her representative as the case may be, within a period of 90 days of receipt of the report of the SAE
   v. The sponsor or its representative shall pay the compensation in case of CT or BA/BE study-related injury, as specified in the order of the CLA within 30 days of the receipt of such order.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.