Scenarios in Medical Ethics-3: New Drugs and Clinical Trials Rules 2019

The new drugs and clinical trial (NDCT) rules 2019 was released on March 19, 2019, by the Central Drugs Standard Control Organization (CDSCO).[1] This was a step toward updating the information about the conduct of clinical trials with new investigational medicinal products in India and the associated regulations surrounding this exercise. According to NDCT Rules 2019, it is mandatory to follow ICMR ethical guidelines for all biomedical and health researches in India. In this issue, we discuss the proceedings of one of the panel discussions that were included as part of the 2-day workshop on medical ethics that was organized for ethics committee members on September 16, 2019 to September 17, 2019 at the Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, in association with ICMR Bioethcs Unit, Bangalore, India.[2,3] It was attended by 80 delegates from 18 institutes. This workshop was planned to train EC members on the ICMR Ethical guidelines for biomedical research on human participants 2017 as well as the NDCT 2019 in addition to having topics of recent relevance such as stem cell research, vaccine research, public health research, and EC registration and accreditation.[1,4]

Six panel discussion sessions were conducted, and each session consisted of a series of 3–6 scenarios followed by 1–3 questions. After presenting each scenario, the participants were invited to give their comments. After a thorough discussion, a set of panelists, who were experts in biomedical ethics, were invited to discuss the scenario and provide more informed and authoritative opinions. The discussions were quite lively and we believe that the case scenarios should be of wider interest.

A summary of the first and second panel discussions on "Composition and Functioning of Ethics Committees" and "Challenges for Ethics Committees" were published previously in this journal. In this article, we discuss the third panel discussion on "NDCT Rules 2019." The answers provided by the participants are listed first followed by the expert opinion by the panelists.

Scenario 1

A novel tyrosine kinase inhibitor has been approved for marketing in India for the treatment of certain forms of hemato-lymphoid cancers. A pharmaceutical company decides to conduct a Phase IV clinical trial at multiple sites in India, and as per the protocol, the duration of treatment with the study drug is 12 months. Sponsors have committed that the participants will have posttrial access to the study drug for at least 1 year or as decided by the Institutional Ethics Committee (IEC) whichever is more.

Questions

i. What are the issues an IEC needs to consider to decide the duration of posttrial access?
ii. Is the sponsor liable for adverse events (AE) that occur during posttrial access?
iii. What do the NDCT Rules 2019 say about posttrial access?

Participant comments

- Posttrial access must be provided by the sponsor even if it is needed lifelong
- Even if the drug is given free of cost, it is the Principal Investigator's (PIs) responsibility to treat any AE that may occur during posttrial period, though the sponsor will not be liable for the AE.

Comments of the panelists

A product is considered as "new drug" for a period of 4 years after approval and posttrial access is applicable for this period following marketing approval.

- The decision to mandate posttrial access must be decided by the IEC after discussion with the PI at the time of protocol review itself. There should be a provision by the sponsor to either provide the drug free of cost or at a subsidized rate after the trial period is over[5]
- If posttrial access needs to be given following Phase II or III trial before marketing decisions, a special permission must be obtained from the licensing authority to use the drug in this small group of participants
- Compensation is applicable for serious adverse events (SAEs) occurring during the trial period only and not beyond that. Consent needs to be obtained from the patient/Legally Accepted/Authorised Representative (LAR) before providing the drug for the posttrial period.

Scenario 2

In a large, investigator-initiated, open-label academic clinical trial, an immunomodulatory treatment (approved for one indication) was being evaluated to improve mortality in intensive care unit (ICU) patients (new indication). It was pointed out that substantial paper work would be involved in reporting SAEs since the expected mortality was >10%. The investigator was of the opinion that SAE reporting is not required for academic clinical trials.

Questions

i. Does SAE reporting framework contained in the NDCT Rules 2019 apply equally well to academic clinical trials?
ii. Should such SAEs be reported to the CDSCO?

iii. Is it mandatory to constitute a Data Safety Monitoring Board (DSMB) in academic clinical trials?

Participant's comment

- All SAEs need to be reported.

Additional question

- If the number of SAEs is very large as in the case with ICU patients, is it necessary to report each and every SAE to the IEC and should the IEC do a causality analysis for all the SAEs?

Comments of the panelists

- According to ICMR 2017 guidelines, SAE reporting in academic clinical trials is similar to regulatory trials as mentioned in NDCT rules 2019, only difference being, in the former, the SAE is reported to the IEC and not to the licensing authority
- DSMB in the regulatory trial is constituted by the sponsor. In case of academic trial, the IEC can decide the need for a DSMB on case-to-case basis. SAEs need to be reported as per the specified timelines to IEC which in turn will evaluate the need for compensation based on the causality analysis. In addition, SAEs must be reported to the DSMB, which in turn will evaluate the participant safety, study conduct, and progress and provide recommendations to the IEC about continuation, modification, or termination of the trial[6]
- All SAEs, whether in a regulatory trial, academic trial or even an observational study need to be reported to the IEC which in turn will do the causality analysis and proceed further as per the guidelines.

Scenario 3

A sponsored clinical trial involving a new drug is being planned in a clinical department of a tertiary care teaching hospital. There is a clause within the Clinical Trial Agreement (CTA) about having insurance for PI negligence. The sponsor insists that it is the PI/Institution's responsibility to take the negligence insurance. However, the institution where the PI works does not have insurance for doctor negligence.

Questions

i. What is the scope of negligence insurance and what should be the coverage limit?
ii. Who should be covered by the negligence insurance-the PI/PI and institute,/PI and trial team members/PI, Ethics committee and Institute?

Participant comment

- Professional indemnity insurance does not cover research-related insurance.

Comments of the panelists

- Deviation from the protocol could be amendment, deviation, or violation. PI negligence can be deviation or violation
- Insurance coverage exists to safeguard the interest of the PI. However, if there is negligence on the side of PI, the insurance cannot cover that. In fact, the CDSCO can inform the MCI about the negligence and the MCI can decide to penalize the PI for negligence
- Since the trial insurance may not cover PI negligence, it is the responsibility of the PI/Institution to obtain insurance cover for legal issues arising over alleged PI/trial team negligence. Such an insurance is available as "errors and omission" policies from standard insurance providers and can be obtained for the PI/Trial team
- Sometimes, in the CTA there is mention of the sponsor covering insurance for the PI, participants as well as the EC. The EC insurance must not be accepted as there is a conflict of interest.

The remaining panel discussions will be discussed in the forthcoming issue.

Acknowledgment

We are thankful to Dr Rakesh Aggarwal for the valuable inputs for both conduct of the workshop and preparation of this manuscript. We wish to acknowledge the resource persons Dr Vasantha Muthusamy, Dr Nandini Kumar, and Dr Bikas Medhi for their valuable contributions as panelists for this session. We also wish to express our sincere gratitude to Dr Roli Mathur and team from ICMR Bioethics Unit for the constant guidance provided and ICMR for funding the workshop.

Financial support and sponsorship

We thank ICMR for partly funding the workshop.

Conflicts of interest

There are no conflicts of interest.

Jayanthi Mathaiyan, Prasanth Ganesan[1], Tamilarasu Kadhiravan[2], Nishanthi Anandabaskar[3]

Departments of Pharmacology, [1]Medical Oncology and [2]Medicine, JIPMER, [3]Department of Pharmacology, Sri Manakula Vinayagar Medical College Hospital, Puducherry, India

Address for correspondence: Jayanthi Mathaiyan, Department of Pharmacology, JIPMER, Puducherry, India.
E-mail: drjayanthi2008@gmail.com

References

1. Ministry of Health and Family Welfare. Available from: https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf. [Last accessed on 2020 Mar 22].
2. ICMR Workshop on ethical guidance for biomedical research. Available from: http://ethics.ncdirindia.org/asset/images/dissemination_images/Puducherry_2019/broucher_JIPMER.pdf. [Last accessed on 2020 Mar 18].
3. Indian Council of Medical Research Bioethics Unit. ICMR NCDIR. Available from: http://ethics.ncdirindia.org//asset/pdf/DisseminationReport2020.pdf. [Last accessed on 2020 Mar 18].
4. Indian Council of Medical Research 2017. Available from: https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf.[Last accessed on 2020 Mar 18].
5. Usharani P, Naqvi SM. Post-trial access. Perspect Clin Res 2013;4:58-60.
6. Zenati MA, Henderson WG. Data Safety Monitoring Board:

Composition and Role. In: Itani K., Reda D, editors. Clinical Trials Design in Operative and Non Operative Invasive Procedures. AG: Springer, Cham; 2017.

Access this article online

Quick Response Code:

Website: www.jpharmacol.com

DOI: 10.4103/jpp.jpp_173_20

How to cite this article: Mathaiyan J, Ganesan P, Kadhiravan T, Anandabaskar N. Scenarios in medical ethics-3: New drugs and clinical trials rules 2019. J Pharmacol Pharmacother 2020;11:148-50.

Received: 24-12-2020 **Revised:** 26-12-2020
Accepted: 29-12-2020 **Web Publication:** 14-05-2021