Original Article

Investigator knowledge, awareness, and registrations of academic clinical trials with the Clinical Trial Registry of India: An observational study

Shruti Bhide[1], Saurabh Patil[1], Amitoj Sohal[1], Neha Kadhe[2], Renuka Munshi[3], Chetan Phirke[1], Snehal Ambre[4], Sudhir Pawar[2], Ruchita Patil[3]

[1]Department of Pharmacology and Therapeutics, Seth GS Medical College and KEM Hospital, [2]Department of Pharmacology, Lokmanya Tilak Municipal Medical College and General Hospital, [3]Topiwala National Medical College and BYL Nair Charitable, [4]Department of Biotechnology, The Institute of Science, Mumbai, Maharashtra, India

Abstract

Introduction: In 2019, the Central Drugs Standard Control Organization (CDSCO) introduced the New Drugs and Clinical Trials Rules 2019 (NDCTR), which separated the research guidelines for "Clinical Trials" and "Biomedical and Health Research." As a result, guidelines issued by *Indian Council of Medical Research* were stated to apply to academic clinical trials (ACTs). This change is important because academic studies are crucial for scientific advancement and repurposing of approved drugs in health-care industry. However, conducting an ACT can pose challenges. We assessed the level of awareness, knowledge, and challenges faced by investigators. Our aim is to overcome some of these challenges and encourage more academic studies for the betterment of healthcare and scientific knowledge in India.

Methodology: The study was conducted in two phases after obtaining approval from the Institutional Ethics Committee (EC) of three tertiary care hospitals in Mumbai. In the first phase, the number of ACTs was assessed from the clinical trial registry India website, while the number of registered and re-registered ECs were assessed from the CDSCO website. The second phase involved assessing investigator awareness and knowledge about ACTs using a prevalidated questionnaire with a content validity index score of 0.93.

Results: In 2020, the highest numbers of studies were registered, with the highest numbers of registered and re-registered ECs from Maharashtra. All participants completed the questionnaire and were aware of the need to follow guidelines for clinical trials. Sixty-seven percent of participants knew that the guidelines for ACTs differed from those of sponsored clinical trials, but only 58% were aware of the exact definition of an ACT as per NDCTR, 2019. Eighty-five percent of participants knew who could initiate an ACT, but only 27% knew about the applicability of results of an ACT and 33% had in-depth knowledge about the required approvals, while only 10% knew the archival period. Although 71% of participants had knowledge about serious adverse event reporting, few answered in-depth questions correctly. Only 31 participants reported facing varied challenges.

Address for correspondence: Dr. Shruti Bhide, Department of Pharmacology and Therapeutics, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India.
E-mail: shrutibhide72@gmail.com

Received: 13-03-23, **Revised:** 26-04-23, **Accepted:** 16-05-23, **Published:** 08-08-23.

Access this article online	
Quick Response Code:	Website: www.picronline.org
	DOI: 10.4103/picr.picr_68_23

How to cite this article: Bhide S, Patil S, Sohal A, Kadhe N, Munshi R, Phirke C, *et al*. Investigator knowledge, awareness, and registrations of academic clinical trials with the Clinical Trial Registry of India: An observational study. Perspect Clin Res 2023;14:187-93.

Conclusion: To conduct ACTs effectively and contribute to healthcare and scientific advancement, it is crucial to enhance investigators' existing knowledge about ACTs.

Keywords: Academic, challenges, ethics, knowledge

INTRODUCTION

Academic clinical trials (ACTs), also known as investigator-initiated studies (IISs), are clinical studies managed by individual physicians/researchers, an institution, or a collaboration of clinical researchers or institutions. Their purpose is purely scientific without any commercial or promotional interest, making them crucial to a country's scientific advancement. IIS covers various studies, such as clinical trials for new drugs and real-world evidence studies that enhance the existing knowledge base and help physicians repurpose drugs and investigate research questions relevant to the current population. They can also contribute to formulating health policies at various levels. These studies are closely related to academic-industry partnerships and promote the development of new drugs and medical products for the market.[1,2]

In India, the Central Drugs Standard Control Organization (CDSCO) is responsible for regulating clinical research. The rules for clinical research are published under the Drugs and Cosmetics Act 1940 and Rules 1945. In 2019, the CDSCO introduced revised rules for clinical trials and biomedical research through the gazette notification of New Drugs and Clinical Trials Rules 2019 (NDCTR). These rules provide guidance for the regulation of clinical trials in India, clearly differentiating between sponsored/regulated clinical trials and ACTs. According to NDCTR 2019, an ACT is a clinical trial of a drug that has already been approved for a specific use but is being tested for a new use, such as a new indication, route of administration, dose, or dosage form. The results of the trial are intended for academic or research purposes only and not for seeking approval from the Central Licensing Authority (which is CDSCO) or any other regulatory authority for commercial purposes.[3]

According to NDCTR, investigators who conduct ACTs should adhere to the 2017 guidelines of the Indian Council of Medical Research (ICMR).[3,4] However, these guidelines have not been updated since 2017 and do not provide complete guidance to investigators on ethical processes, including submission to Ethics Committees (ECs) and monitoring, medical management of participants, and compensation processes in self-funded ACTs. The densities and facts (global and Indian) involved in the various aspects of ACTs have already been elaborated immediately after the publication of NDCTR.[5]

Since the conduct of ACTs involves complex issues[6] and no research has been conducted to assess the knowledge and awareness of investigators about ACTs, this study was designed to explore the investigators' knowledge, awareness, and challenges related to ACTs.

METHODOLOGY

The study was commenced after obtaining approval from the Institutional ECs of the three tertiary care hospitals of Mumbai.

The study was conducted over 6 months in two phases. In Phase 1, Clinical Trial Registry India (CTRI) database was used to assess the number of academic interventional studies registered with CTRI from April 2019 to October 2022 and to analyze their sources of funding. The number of registered and provisionally registered ECs under the Department of Health Research (DHR) and CDSCO as of December 2022 was also assessed to find the number of ECs registered under DHR for the review of studies related to Biomedical and Health Research and ACTs. Phase 2 used a questionnaire-based study design and assessed the knowledge and awareness about ACTs among academicians, using a prevalidated questionnaire. Another objective was to assess the practical experience and challenges that investigators faced in the conduct of ACTs.

A formal calculation to determine the number of participants needed was not done. Qualified principal investigators (PIs) from three tertiary care hospitals willing to participate in the study and complete a validated questionnaire either online or on paper were invited. We were able to meet an arbitrary set goal of 100 responders.

During Phase 1 of data collection, the CTRI website (https://ctri.nic.in/Clinicaltrials/login.php) was accessed on November 10, 2022, to collect the information on the type of study and funding agency.[7]

Under "Trial Search," the fields and keywords were selected as:

Prospective/Retrospective Trials-"Prospective," Type of Trial-"Interventional," Month and Year of Trial registration-From "April 2019 to October 2022," Type of study-"Drug" and for Primary Sponsor-"Research Institution" and "Research Institution and Hospital" (clubbed for analysis), "Government funding agency" and "Government Medical College" (clubbed for analysis), "Private Medical College" and "Private hospital/clinic" (clubbed for analysis).

The website www.naitik.gov was also accessed to collect the information on registered ECs under DHR and https://cdsco.gov.in was accessed for CDSCO registration.[8,9] In Phase 2, a prevalidated questionnaire was used to collect the data with a Scale-Level Validity index of 0.93.[10]

The questionnaire used in the study had 22 questions that aimed to assess different areas related to ACTs. The questions were divided into four domains: Awareness, knowledge, practical experience, and challenges faced.

In the awareness domain, the questions required a Yes/No response and focused on various guidelines and requirements related to ACTs. The knowledge domain included questions related to general knowledge, guidelines, and knowledge about serious adverse events (SAEs). The practical experience questions required a Yes/No response, while the questions related to challenges faced were open-ended and qualitative.

The data collected from both phases were analyzed using the descriptive statistics in Microsoft Excel. The responses given by participants were categorized as correct, incorrect, partially correct, or no response, and then expressed as percentages.

RESULTS

Phase 1

The number of academic interventional studies registered at CTRI was the highest in 2020 among the time period from April 2019 to October 2022. Studies funded by Research Institutes/Institutions and Hospitals had the highest number of registrations followed by government funding agency studies, while studies funded by private medical colleges/hospitals/clinics had the lowest number of registrations [Figure 1].

There were 658 ECs provisionally registered at DHR. The highest number of provisionally registered ECs was from Karnataka, followed by Tamil Nadu, Maharashtra, Telangana, Kerala, and Gujarat. However, only 168 of these ECs had final registration at DHR, with the highest number of registered ECs in Maharashtra. The study also revealed that the registration of 161 ECs had expired, and therefore, needed to be re-registered [Figure 2]. Maharashtra had the highest number of committees, both institutional and independent, registered [Figure 3].

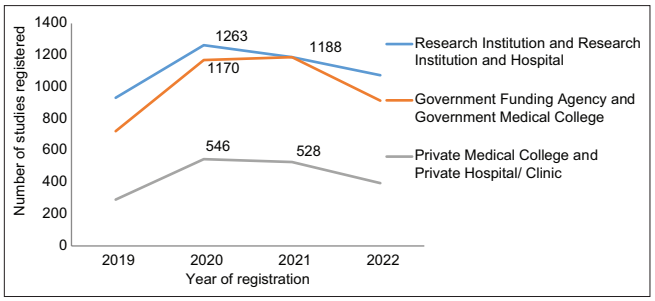

Figure 1: Year wise trend in academic interventional studies and funding type

Phase 2

Awareness

In this study, 100 participants completed the questionnaire and gave their consent. All participants knew about the guidelines and rules for conducting a clinical trial, but only 67% were aware that guidelines and rules for ACTs are different from sponsored clinical trials. Fifty-eight percent of participants knew the exact definition of an ACT as per NDCTR, 2019. Eighty percent knew that an insurance policy is required for conducting an ACT, while only 15% were aware that a drug import license is not required. Only 16% of participants knew which documents are required to conduct an ACT.

Knowledge

Eighty-five percent of participants correctly mentioned that an ACT can be initiated by an investigator, academic or research institute. However, only 30% knew that an ACT can be conducted for an already approved drug (a drug that has been approved for more than 4 years, excluding biologicals/boisimilars) with a different formulation or a change in dose, dosage form or route of administration. In addition, only 27% of participants knew that data obtained from an ACT can be used for academic and research purposes only. Regarding ACT approval, 33% of participants answered the queries correctly. Only 10% of participants knew that the documents of an ACT must be archived for 3 years, as shown in Table 1.

In addition, the study found that 52% of participants were able to name at least one guideline for the conduct of clinical trials in India. However, 24% gave incorrect answers and another 24% provided no response at all. In contrast, only 17% of participants were able to correctly

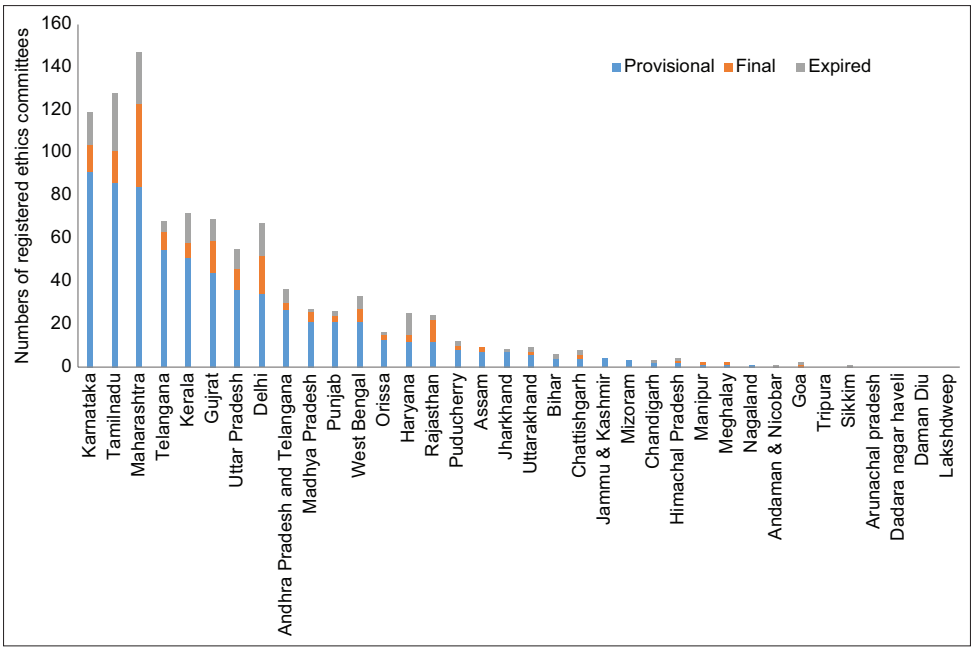

Figure 2: Number of Ethics committees registered at DHR. DHR: Department of Health Research

Table 1: Domains of knowledge and response recorded

Knowledge domain	Question	Correct responses (%)	Incorrect responses (%)	Partly correct responses (%)	No response
General	A trial can be called ACT if initiated by	85	15	-	-
	An ACT can study this/these entity/entities	30	42	28	-
	The results obtained from an ACT can be used for	27	66	7	-
	An ACT requires approval from	33	67	-	-
	For how many years, documents of an ACT need to be stored/ archived?	10	83	-	7
Guideline specific	Can you name at least one guideline which is to be followed in India while conducting a clinical trial?	52	24	-	24
	Which guidelines need to be followed for conducting an ACT?	17	20	14	49
	In line with New Drugs and Clinical Trial Rules, 2019; what type of studies fit the definition of ACT?	15	12	73	-
	When will an ethics committee communicate with DCGI before approving your ACT?	2	19	-	79
SAE and compensation	SAE occurring in an ACT needs to be reported to	71	24	5	-
	Who decides the amount of money to be paid as compensation to participant in case of SAE?	3	35	42	20
	Who provides the compensation?	28	51	5	16

SAE=Serious adverse event, ACT=Academic clinical trial, DCGI=Drugs Controller General of India

name guidelines for the conduct of ACT, with 14% giving partially correct responses and a whopping 49% giving no responses at all.

Moreover, only 15% of participants correctly responded that, in line with NDCTR 2019, only interventional studies fit in the definition of ACT.

Regarding the communication between ECs and Drugs Controller General of India (DCGI), 41% of participants were aware that the EC may communicate with the DCGI before approving an ACT. However, only 2% of participants could correctly specify a situation where EC may communicate with the DCGI.

Finally, the study highlighted the need for better understanding of the reporting of SAEs in ACT. While 71% of participants correctly answered that SAEs need to be reported to the Chairperson of EC and DCGI/Central Licensing Authority, only 3% and 28% of participants could specify who decided the quantum of compensation and who would be responsible for paying it, respectively.

Practical experience

Eighty-nine percent of the participants reported that they had received some training specific to conducting ACTs. However, only 41% of the participants had been involved in at least one ACT, with 48% having no experience in this area. This indicates that while the majority of participants

had some level of training, actual experience with ACTs was relatively low, as shown in Table 2.

Challenges faced during the conduct of an academic clinical trial

Out of the 41 participants who had experience conducting ACTs, 31 of them shared the challenges they faced during the process. Among these participants, 8 had issues related to obtaining approval from the EC, while 5 participants faced challenges with participant recruitment and migration. Four participants faced difficulties related to funding, and two participants reported time constraints. Furthermore, twelve participants experienced multiple challenges related to logistics, technical issues, monitoring, and collaboration during the conduct of their ACTs.

DISCUSSION

Our study sheds light on the awareness levels among participants concerning ACTs in India. The data show that a substantial number of ACTs, around 2383, are currently ongoing in India. Although our study found that the majority of participants were familiar with the existence of separate guidelines and rules for ACTs and the insurance policy requirements associated with it, the awareness levels about certain important aspects of ACTs were modest. For example, knowledge regarding the role of the Drugs Controller General of India (DCGI) in the approval process and drug import regulations related to ACTs was limited. In addition, our data also suggest that familiarity with the guidelines associated with ACTs was modest among participants.

The funding of clinical trials in India has been reported to be mostly provided by the pharmaceutical industry.[11] In a recent audit from 2007 to 2018, it was found that 86.3% of regulatory interventional studies registered on the CTRI website were sponsored by the Pharma industry, followed by 7.3% by the Government, 0.7% by Private medical colleges, and 5.8% by other sponsors, including PI-initiated studies. In our study, we focused on studies that could fall under the ACT category, without separating the sponsorship for PI-initiated clinical trials, since they could be sponsored by any of the above-mentioned sponsors. We found that most of the ongoing research in this category was supported by research institutes, followed by government bodies and private medical colleges. Such meagre numbers of academic research projects being conducted in India may be attributable to one or more of several reasons such as limited knowledge and awareness about ACTs, financial constraints, lack of trained workforce and expertise in research methodology, and time constraints, as discussed by Bavdekar and Karande.[6]

NDCTRs prohibit the commercial and promotional use of data obtained from an ACT. This means that the pharmaceutical industry may not be willing to sponsor academic trials that do not offer commercial benefits. In the absence of such funding, academic trials face financing challenges, unless the investigator can secure alternative sources of funding from governmental or institutional sources. Moreover, the investigator must ensure that the legal agreement with the funding company includes a clause that prohibits current or future commercial or promotional use of results in India. This adds to the legal responsibilities of the investigator. It is also imperative for an investigator to be aware of the concept of subsequent new drugs (SNDs).[12] An SND (Subsequent New Drug) application is used for drugs that have been approved within the last four years by the Central Licensing Authority (CLA)/CDSCO under Rule 21, and are now proposed to be marketed with modified or new claims such as indications, dosage, dosage form (including sustained release dosage form), and route of administration. On the other hand, an ACT cannot be used for marketing approval for a new claim of an already approved drug.

Table 2: Practical experience questions and their responses

Question	Response	
	Number of trials	Number of respondents
How many ACTs have you conducted/ presently undertaking?	0	48
	1–3	30
	4–6	10
	>6	1
	Unclear/ no response	11
Have you received any training specifically directed toward undertaking an ACT?	Yes=89, no=11	
Did you face any challenges while conducting an ACT?	Yes=31 (out of 41 who undertook ACT)	

ACT=Academic clinical trial

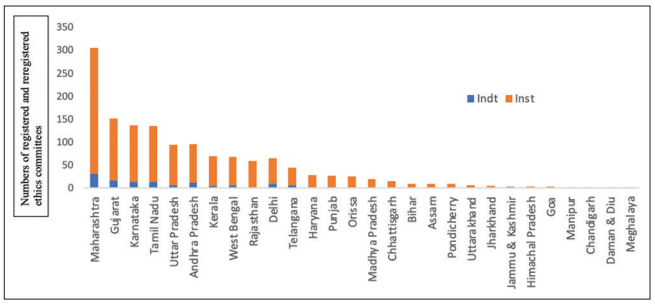

Figure 3: Number of ethics committees registered and re-registered at CDSCO. CDSCO: Central Drugs Standard Control Organization, Indt: Independent Ethics Committees, Inst: Institutional Ethics Committees

According to Bavdekar and Karande, some investigators mentioned that EC related issues were a challenge in conducting ACTs.[6] This suggests that investigators face difficulties related to the ethics approval process. In order to address these issues and find solutions, it is important to understand the nature of the challenges. In addition, the study found that only a few investigators had experience in conducting ACTs, indicating a lack of knowledge about ACTs among investigators. Therefore, if we are to make scientific progress that is independent of commercial interests, it is imperative to provide training at an early stage to investigators for conducting ACTs, and to formulate and implement clear guidelines and standard operating procedures for the conduct of ACTs.

The purpose of evaluating the number of studies that may fall under ACTs was to determine how many institutions and investigators were conducting them. The results show that the highest number of registered ACTs was in 2020, followed by a declining trend, which is possibly partially attributable to COVID-19 pandemic. As of April 2019 (according to the NDCTR, 2019), there were 1400 ECs registered and re-registered with CDSCO, with the majority located in Maharashtra. In addition, 658 ECs were re-registered with DHR, also with the highest number from Maharashtra. In a 2019 survey conducted by Das and Singh, it was found that out of the 911 ECs eligible for re-registration, only 516 (56.5%) had re-registered.[13] This low proportion of eligible ECs that were re-registered may have several reasons, which require further exploration.

During the study, it was observed that participants were aware of the requirement to report SAEs to the Chairperson of the EC and to the Drug Controller General of India (DCGI)/Central Licensing Authority. However, there was limited knowledge about who decides on and pays for compensation in case of SAEs. EC-related challenges were commonly faced by the participants. Bavdekar and Karande have also highlighted the challenges in insurance and compensation for ACTs.[6] However, one key issue is that the ICMR 2017 guidelines do not provide clear guidance on how to calculate the compensation amount. This poses a unique challenge when estimating the compensation amount required for any ACT. Furthermore, the ICMR guidelines suggest that participants in the control group should be compensated, which differs from the NDCTR 2019 guidelines.[4,5] The absence of assistance from the legal department also raises concerns about estimating insurance premiums. Other important factors to consider when conducting an ACT include the allocation of funds for free medical management and compensation for research-related injuries, patient travel and inconvenience, ancillary care, and postresearch access. The compensation guidelines can impose a significant financial burden on institutions or demotivate researchers from conducting ACTs. These challenges can also drive researchers towards observational studies rather than interventional studies.[5] Although in this study we did not explore in detail the challenges faced by investigators. Few ACTs being conducted reflect a need for increased opportunities for practical training and experience in conducting ACTs to help bridge the gap between knowledge and practice. We looked at the number ECs registered at CDSCO and DHR. These ECs may also need training for review of ACTs, although we haven't looked at this aspect in this study as emphasised by Bhatt.[5]

In summary, this study aimed to identify the reasons behind the low number of ACTs and biomedical research in India. The findings suggest that a lack of awareness and knowledge about ACTs, as well as challenges related to ECs, insurance and compensation, and allocation of study funds, may be contributing to this issue. It is clear that more research is needed to gain further insights into these challenges at the local level, and to develop solutions that will encourage more academic studies in India.

Strengths and limitation

This study may be the first of its kind to evaluate the understanding and familiarity of ACTs among researchers. However, we acknowledge that our research has some limitations, such as the relatively small sample size and the fact that the study was conducted only at three tertiary care centers in Mumbai. Therefore, the findings of this study may not be representative of the level of knowledge and awareness across the entire country. There were discrepancies noted during data retrieval from CTRI website such as missing details of PI in some cases. Some government funded studies having pharmaceutical industry as secondary sponsor which may create overlap and may not fit definition of ACTs strictly.

CONCLUSION

Although a significant number of participants were aware of the guidelines and rule for conducting clinical trials, there was a lower level of awareness of guidelines and rules specifically pertaining to ACTs. In addition, there were several gaps in knowledge regarding the documents required, approval processes, and reporting of adverse events in ACTs. Furthermore, challenges faced during the conduct of ACTs were primarily related to EC-related issues, participant recruitment, funding, and logistics. These findings highlight the need for targeted training

and education on the specific guidelines, rules and requirements for the conduct of ACTs, as well as the need for stakeholders to address the challenges faced by researchers during the conduct of these trials.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Konwar M, Bose D, Gogtay NJ, Thatte UM. Investigator-initiated studies: Challenges and solutions. Perspect Clin Res 2018;9:179-83.
2. Suvarna V. Investigator initiated trials (IITs). Perspect Clin Res 2012;3:119-21.
3. New Drugs and Clinical Trials Rules; 2019. Available from: https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdfdocuments/NewDrugs_CTRules_2019.pdf. [Last accessed on 2023 Feb 01].
4. National Ethical Guidelines for Biomedical and Health Research Involving Human Participants. Indian Council for Medical Research; 2017. Available from: https://main.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf. [Last accessed on 2023 Feb 01].
5. Bhatt A. New clinical trial rules: Academic trials and tribulations. Perspect Clin Res 2019;10:103-5.
6. Bavdekar SB, Karande S. National ethical guidelines for biomedical and health research: Issues to ponder over. J Postgrad Med 2022;68:125-8.
7. Clinical Trials Registry – India. Available from: https://ctri.nic.in/Clinicaltrials/advsearch.php. [Last accessed on 2022 Nov 10].
8. Ethics Committee Registered with NECRBHR, DHR. Available from: https://naitik.gov.in/DHR/app_srv/soam/reports_pc_issued.jsp. [Last accessed on 2022 Nov 10].
9. List of Registered/Re Registered Ethics Committee. Available from: https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/ecddec22.pdf. [Last accessed on 2023 Feb 01].
10. Yusoff MS. ABC of content validation and content validity index calculation. Educ Med J 2019;11:49-54.
11. Rao MV, Maulik M, Juneja A, Adhikari T, Sharma S, Gupta J, *et al*. Clinical trials registry – India: A decadal perspective. Indian J Pharmacol 2020;52:272-82.
12. Subsequent New Drugs – CDSCO. Available from: https://cdsco.gov.in/opencms/opencms/en/Drugs/Subsequent-New-Drugs/. [Last accessed on 2023 Feb 01].
13. Das MK, Singh D. Ethics committee registration and re-registration with the regulatory authority in India. Natl Med J India 2019;32:157-60.