Research in Health & Medical Sciences *Original Article*

2023 December; 2(4)

A Comprehensive Analysis of Ethical Issues in Clinical Trials

Kourosh Delpasand[1], Yashar Rahnamanejad[2], Saman Maroufizadeh[3], Morteza Rahbar-Taramsari[4], Saeed Biroudian[5]*

[1] Department of Medical Ethics, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.
[2] Razi Clinical Research Development Unit, Razi Hospital, Guilan University of Medical Sciences, Rasht, Iran
[3] Department of Biostatistics and Epidemiology, School of Health, Guilan University of Medical Sciences, Rasht, Iran
[4] Department of Forensic Medicine, School of Medicine, Razi Hospital, Guilan University of Medical Sciences, Rasht, Iran
[5] Department of Medical Ethics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

***Corresponding Author Email: sbiroudian@gmail.com**
Received: 2025/7; Revised: 2025/9; Accepted: 2025/11

Abstract

Ethical standards in clinical trials are essential to safeguard human participants and ensure scientific credibility. Despite global frameworks such as the Declaration of Helsinki and national reforms in Iran, evidence suggests ongoing ethical deficiencies in trial documentation and conduct.

The objective of this study is to systematically examine and evaluate the ethical issues that arise in clinical trials. This analysis aims to identify common ethical challenges, assess current guidelines and regulatory frameworks, and propose recommendations to enhance the ethical conduct of clinical research. By providing a comprehensive overview, the study seeks to promote greater awareness and understanding of ethical considerations among researchers, participants, and policymakers involved in clinical trials.

This retrospective descriptive study analyzed all clinical trial proposals approved by Guilan University of Medical Sciences between January 2018 and December 2022. Using a structured checklist, data were extracted on investigator demographics, faculty affiliation, clinical discipline, inclusion of informed consent forms, use of placebo, and treatment deprivation.

A total of 219 proposals were reviewed. Only 137 (62.5%) of trials included an informed consent form, 26 (11.9%) used a placebo, and 11 (5%) involved deprivation from standard treatment, highlighting notable gaps in ethical documentation. Most studies were submitted in 2018, 64 (29.2%), and were affiliated with the Faculty of Medicine, 146 (66.7%). Male researchers were the majority, 119 (54.3%). Nursing, anesthesiology, and obstetrics & gynecology were the most active fields. Ethical documentation varied significantly across disciplines.

Despite national-level improvements in Iran's research ethics infrastructure, considerable gaps remain at the institutional level. Targeted efforts are needed to enhance ethical training, strengthen review processes, and ensure consistent adherence to international standards across all disciplines.

Keywords: Clinical Trials as Topic, Ethics, Research, Informed Consent, Placebos, Ethics Committees

Introduction

Clinical trials are critical to advancing modern medicine and ensuring patient care is rooted in evidence-based interventions (1). They provide a structured pathway for testing new treatments, diagnostics, and preventive strategies, directly influencing healthcare policy and practice. However, the conduct of clinical trials demands strict ethical oversight, as it inherently involves risks to human participants, including physical, psychological, and social harms. Ethical lapses in research history, from the Tuskegee Syphilis Study to controversial consent practices in modern international trials, have prompted global efforts to enforce stricter guidelines (2, 3).

Internationally recognized ethical frameworks such as the Declaration of Helsinki, the Belmont Report, the CIOMS guidelines, and directives from the World Health Organization (WHO) have been developed to safeguard participants' rights and welfare (4). These documents emphasize core principles, including voluntary informed consent, scientific validity, fair selection of participants, risk-benefit assessment, and independent ethical review. Among these, the role of informed consent has evolved significantly from a one-time signature to an ongoing ethical process that ensures participants' autonomy is continuously respected (5).

Despite regulatory advancements, empirical data indicate persistent shortcomings: about 30% of randomized trials fail to obtain valid informed consent, and risks associated with placebo use are often inadequately disclosed (6, 7). Moreover, the COVID-19 pandemic introduced additional ethical challenges, including accelerated approvals and limits on participant autonomy, generating renewed scrutiny of established safeguard mechanisms (8).

The translation of these global ethical principles into local practice varies significantly, particularly in low- and middle-income countries. In Iran, efforts to improve ethical compliance have intensified in recent years. The establishment of the National Research Ethics Committee in 2010 marked a significant milestone in the standardization of ethical review procedures across the country. However, disparities remain at the institutional level. Studies conducted in various Iranian medical universities have identified gaps in documentation, such as partial omission of informed consent forms and vague reporting of placebo or treatment withholding protocols (9-12). These inconsistencies pose significant ethical challenges, particularly in ensuring transparency and protecting vulnerable populations.

These inconsistencies pose significant ethical challenges, particularly in ensuring transparency and protecting vulnerable populations.

While previous studies in Iran have highlighted general ethical challenges, there is a scarcity of detailed, institution-specific analyses focusing on key ethical indicators over a sustained period. This study aims to fill this gap by providing a comprehensive, longitudinal analysis of ethical documentation in clinical trials at Guilan University of Medical Sciences. It focuses specifically on three sensitive and critical ethical benchmarks: informed consent documentation, placebo use, and treatment deprivation strategies. By analyzing these indicators from 2018 to 2022, this research seeks to provide a clearer picture of ethical compliance trends and contribute to broader efforts aimed at strengthening research ethics and promoting accountability in human subject research in Iran and similar contexts (13).

This study aims to systematically examine the existing ethical dimensions in clinical trials approved by Guilan University of Medical Sciences from 2018 to 2022. The main focus is on evaluating three key indicators: documentation of informed consent, use of a placebo, and application of treatment deprivation. The findings of this research can provide a deeper understanding of current ethical trends and contribute to improving research policies and ethics education at the national level.

Material and Methods

This retrospective descriptive study was conducted at Guilan University of Medical Sciences and approved by the university's Research Council and Ethics Committee (Ethics ID: IR.GUMS.REC.1401.563). All clinical trial proposals registered via the National Ethics Committee's online platform between January 2018 and December 2022 were screened for eligibility. Proposals with incomplete data or lacking access permission were excluded.

A structured checklist was used to extract data. The checklist was developed based on Iran's National Research Ethics Guidelines and core principles of Good Clinical Practice (GCP). To ensure clarity, consistency, and reproducibility during the evaluation process, the following key variables were explicitly defined for the auditors:

Informed Consent Form: This was defined as the presence of a dedicated, signable form within the proposal documents that explicitly outlined the study's purpose, procedures, potential risks and benefits, and emphasized the voluntary nature of participation.

Placebo Use: This was recorded as 'yes' only if the study protocol explicitly described the administration of an inert substance or intervention to a control group.

Treatment Deprivation: This was defined as the intentional withholding of a known, effective standard treatment from the control group for the entire duration of the study, where such a standard treatment existed for the condition under investigation.

A structured checklist was used to extract data on year of submission, gender, and faculty affiliation of the principal investigator, clinical discipline, inclusion of informed consent forms, use of placebo, and treatment deprivation. Faculty fields were categorized by department (e.g., Nursing, Dentistry, Anesthesiology, and Obstetrics & Gynecology).

To minimize information and selection bias, two independent reviewers assessed each proposal using a standardized checklist with clear operational definitions. However, a potential limitation is that the study relied on documentation within the proposals and did not verify practices during the actual conduct of the trials or in subsequent publications.

Raw data were initially entered and managed in Microsoft Excel. Analyses were performed using SPSS version 16. Descriptive statistics were used for both categorical and continuous variables. Categorical data (e.g., faculty distribution, informed consent presence) were reported as frequencies and percentages; continuous variables as means ± standard deviations. Yearly trends were explored using chi-square tests where applicable.

Results

Of the 250 proposals initially identified, 31 were excluded due to incomplete data in the online registry or lack of access permission for full-text review. Consequently, 219 proposals met the inclusion criteria and were analyzed. Among these, the highest number of proposals, 64 (29.2%), were submitted in 2018. Most principal investigators were male, 119 (54.3%), and the majority of studies were affiliated with the Faculty of Medicine, 146 (66.7%), followed by Nursing and Midwifery, 38 (17.3%), Dentistry, 30 (13.7%), and Pharmacy, 4 (1.8%) (Table 1). Only 137 (62.5%) of trials included an informed consent form, 26 (11.9%) used a placebo, and 11 (5%) involved deprivation from standard treatment, highlighting notable gaps in ethical documentation.

The most active clinical fields were Nursing, 33 (15.1%), Anesthesiology and Obstetrics & Gynecology, 24 (each 10.9%), and Surgery, 20 (9.1%), with further details provided in Table 2.

Figure 1 illustrates the annual trend of clinical trial proposals from 2018 to 2022 in Guilan province. The chi-square test for trend indicated that this distribution was stable over time (p-value = 0.85). This p-value confirms that there was no statistically significant increasing or decreasing trend in the number of proposals during the study period.

Variable	Category	N (%)
Researcher's gender	Male	119 (54.3)
	Female	100 (45.7)
Faculty	Nursing and Midwifery	38 (17.3)
	Public Health	1 (0.5)
	Medicine	146 (66.7)
	Dentistry	30 (13.7)
	Pharmacy	4 (1.8)
Informed Consent Form (n)	Yes	137 (62.5)
	No	82 (37.5)
Placebo	Yes	26 (11.9)
	No	203 (88.1)
Deprivation from Treatment	Yes	11 (5)
	No	208 (95)

Table 1. The clinical data of the clinical trial studies (N=219)

Faculty	Major / Field	N (%)
Paramedicine	Public Health	1 (0.5)
	Reproductive Health	2 (0.9)
	Nursing	33 (15.1)
	Biotechnology	2 (0.9)
	Tissue Engineering	1 (0.5)
Pharmacy		4 (1.8)
Dentistry		30 (13.7)
Medicine	ENT (Ear, Nose, Throat)	8 (3.6)
	Orthopedics	4 (1.8)
	Urology	4 (1.8)

	Anesthesiology	24 (10.9)
	Nutrition	5 (2.3)
	Surgery (all surgical fields combined)	20 (9.1)
	Ophthalmology	9 (4.1)
	Internal Medicine (all internal fields combined)	10 (4.6)
	Psychiatry	5 (2.3)
	Obstetrics and Gynecology	24 (10.9)
	Emergency Medicine	2 (0.9)
	Anatomy	1 (0.5)
	Physiotherapy	5 (2.3)
	Cardiology	11 (5.0)
	Pediatrics	10 (4.6)
	Neurology	4 (1.8)

Table 2. The faculty of each clinical trials study in Guilan province (N=219)

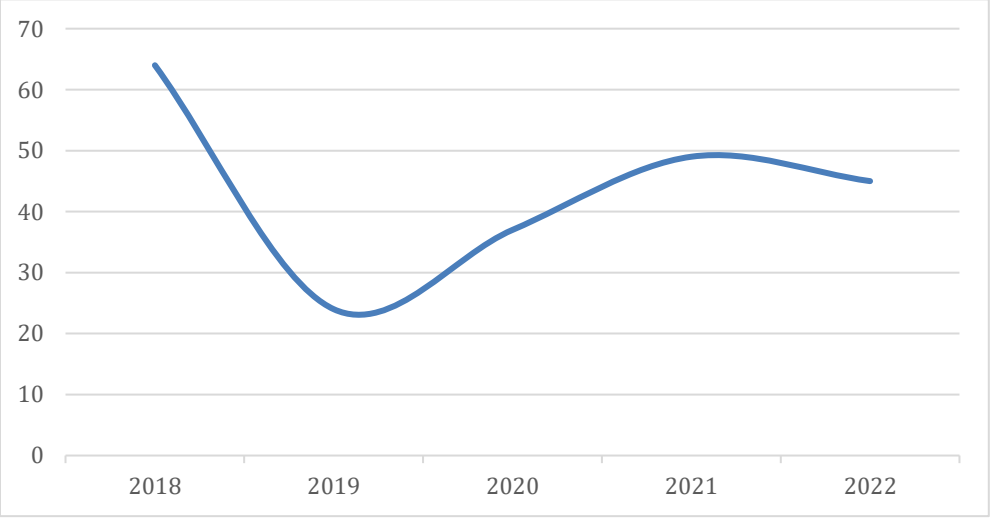

Figure 1. The trend of clinical trials during 2018- 2022 in Guilan province

Discussion

Phase III clinical trials are the final stage of medical research and play a crucial role in scientific advancement and improving healthcare (14-16). Adherence to ethical principles in these studies—including honesty, justice, obtaining informed consent, protecting participants' rights, and maintaining confidentiality—is essential for preserving human dignity and scientific credibility (17-20).

Findings from this study revealed that only 62.5% of proposals included informed consent forms, indicating significant deficiencies in ethical documentation. Additionally, placebo use in 11.9% and deprivation of standard treatment in 5% of cases are issues requiring greater attention. Possible reasons for these shortcomings include lack of ethics training, inadequate oversight, or cultural and organizational differences, which merit further investigation.

Research activities were primarily concentrated in the School of Medicine (66.7%) and Nursing (17.3%), consistent with the overall trend of research in Iran. The annual trend of proposals in Guilan Province from 2018 to 2022 remained relatively stable, which may indicate consistency in research policies and ethical oversight. However, stability does not imply completeness, and continuous monitoring and evaluation are necessary.

However, this study has several limitations. First, it relied solely on documentation within research proposals approved by the ethics committee. It is possible that some researchers addressed ethical components during the actual conduct of the trial but failed to document them adequately in the initial proposal. Conversely, the presence of a document does not guarantee its proper implementation. Second, we did not track the subsequent publications arising from these proposals to verify if ethical practices like informed consent were reported in the final articles. Third, the study was conducted in a single university, which may limit the generalizability of findings to other institutions in Iran or other countries, though it provides a detailed institutional case study.

Conclusion

Despite national advances in ethical policies, this study shows significant gaps in the documentation and implementation of research ethics at the institutional level. Lack of transparency regarding placebo use and treatment deprivation, along with inconsistent use of informed consent forms, are areas requiring immediate improvement. To enhance the situation, it is recommended that ethics committees be strengthened, continuous training for researchers be provided, and structured checklists be mandatorily applied during proposal review processes. These actions can help increase compliance with international standards and foster a sustainable, ethical research culture in clinical studies in Iran and other resource-limited countries.

Conflict of Interests

The authors declare no conflict of interest.

References

1. McNair L. Ethical and regulatory oversight of clinical research: The role of the Institutional Review Board. Exp Biol Med (Maywood). 2022;247(7):561-6.
2. Ataullahjan A, Lo S, Aziz MH, Somani NA, Bhutta ZA. Why we need stricter oversight of research involving human subjects affected by conflict. AMA journal of ethics. 2022;24(6):518-29.
3. Kass NE, Faden RR, Angus DC, Morain SR. Making the ethical oversight of all clinical trials fit for purpose. JAMA. 2025;333(1):75-80.
4. Association WM. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama. 2013;310(20):2191-4.
5. Cavaleri M, de Sousa CMA, Hacker A, Higgs ES, Lumpkin MM, Maia CS, et al. A roadmap for fostering timely regulatory and ethics approvals of international clinical trials in support of global health research systems. The Lancet Global Health. 2025;13(4):e769-e77.
6. Dewar-Haggart R, Muller I, Bishop F, Geraghty AW, Stuart B, Kendrick T. Predicting

intentions towards long-term antidepressant use in the management of people with depression in primary care: A longitudinal survey study. Plos one. 2025;20(3):e0299676.

7. Blease CR, Bishop FL, Kaptchuk TJ. Informed consent and clinical trials: where is the placebo effect? Bmj. 2017;356:j463.

8. Vitti JN, Vitti R, Chu K, Mellis S. The ethics of clinical research in the era of COVID-19. Frontiers in Public Health. 2024;12:1359654.

9. Aramesh K. A Brief History of Biomedical Research Ethics in Iran: Conflict of Paradigms. Dev World Bioeth. 2015;15(2):107-12.

10. Mansoori P. Evolution of Iran's health research system over the past 50 years: a narrative review. J Glob Health. 2018;8(2):020703.

11. Fakour Y, Eftekhari MB, Haghighi Z, Mehr NK, Hejazi F. Situation analysis of local ethical committees in medical sciences in Iran. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2011;16(3):310.

12. Mohamadi A, Asghari F, Rashidian A. Continuing review of ethics in clinical trials: a surveillance study in Iran. Journal of Medical Ethics and History of Medicine. 2014;7:22.

13. Hyder AA, Wali SA, Khan AN, Teoh NB, Kass NE, Dawson L. Ethical review of health research: a perspective from developing country researchers. Journal of medical ethics. 2004;30(1):68-72.

14. Cortegiani A, Absalom AR. Importance of proper conduct of clinical trials. British Journal of Anaesthesia. 2021;126(2):354-6.

15. Ahmed I, Ishtiaq S. Reliability and validity: importance in medical research. Methods. 2021;12(1):2401-6.

16. Li H, Moon JT, Purkayastha S, Celi LA, Trivedi H, Gichoya JW. Ethics of large language models in medicine and medical research. The Lancet Digital Health. 2023;5(6):e333-e5.

17. Ehidiamen AJ, Oladapo OO. Enhancing ethical standards in clinical trials: A deep dive into regulatory compliance, informed consent, and participant rights protection frameworks. World Journal of Biology Pharmacy and Health Sciences. 2024;20(1):309-20.

18. Kandi V, Vadakedath S. Ethical considerations in clinical research: a comprehensive review. American Journal of Public Health Research. 2022;10(2):42-52.

19. Raj GM. Ethical issues related to medical research on human participants. Introduction to Basics of Pharmacology and Toxicology: Volume 3: Experimental Pharmacology: Research Methodology and Biostatistics: Springer; 2022. p. 819-37.

20. Young MJ, Bodien YG, Edlow BL. Ethical considerations in clinical trials for disorders of consciousness. Brain Sciences. 2022;12(2):211.