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Review Article: Ethical Considerations in Conducting Clinical Trials

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ABSTRACT

Background: Clinical trials are the golden key in medical science research with human participants. They have always been considered interesting topics by researchers and scientists working in this field. However, the samples are "human participants," so the research should be carefully conducted.

Methods: In the present study, the published articles on the ethical challenges of conducting clinical trials were evaluated between 2010 and 2019 in Google Scholar, PubMed, and Scopus. The English search keywords were "clinical trial," with at least one of the phrases of "ethical consideration" or "standard".

Results: In this article, we examined the ethical requirements and considerations in these research studies in four stages: research design and question, proposal review and approval, supervision and implementation, and publication of the results. We have examined them using relevant articles published between 2010 and 2019 and identified important and prominent issues or neglected ones.

Conclusion: During this study, it was found that the "research design and question" stage was the most discussed and challenging stage, and the authors' sensitivity about it has been more than the other three stages. On the other hand, the "results publishing" stage has been considered less sensitive with the least number of references in articles.

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1. Introduction

Clinical trials are the golden key for human research to advance medical science, find new medications and design modern therapies. According to the definition of the World Health Organization, "clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Clinical trials may also be referred to as interventional trials. Interventions include but are not restricted to drugs, cells, and other biological products, surgical procedures, radiologic procedures, devices, behavioral treatments, process-of-care changes, preventive care, etc" [1].

In the last century, with the discovery of new drugs and the advancement of medical sciences, the need for research to determine the efficiency or effectiveness of drugs and scientific methods and more knowledge of the human body has dramatically increased. So, this type of research has always been of interest to scientists and ethicists due to the involvement of human subjects.

The classic examples of this research that led to significant sensitivity are Tuskegee research, recognition of the effects of sulfonamides, how malaria is transmitted to prisoners of war in German camps, Japanese experiments to discover the plague vaccine, etc. These trials led to the Nuremberg Codes, the Helsinki Declaration, and the Belmond Report.

In the 1970s, the need for a rigorous technical, standard, and ethical oversight of this type of research led to the establishment of the Pharmaceutical Manufacturer Association (PMA) or the Food and Drug Administration (FDA) in various countries.

Over time, new instructions and regulations have been revised and prepared to conduct clinical trials more scientifically and ethically. However, there seem to be differences between what was done and what will be done. So in many cases, there are challenges in how to perform the clinical trials and adhere to the instructions.

This paper collects and evaluates published articles on the ethical challenges of clinical trials between 2010 and the end of 2019 and classifies them into different sections.

2. Materials and Methods

In the present study, the published articles on the ethical challenges of conducting clinical trials were evaluated between 2010 and 2019. The articles were searched for their title and content in web-based search engines, including Google Scholar, PubMed, and Scopus. The English search keywords were "clinical trial", with at least one of the phrases of "ethical consideration" or "standard" in a purposeful and advanced search (searching the titles and abstracts). Persian equivalent words were searched in SID, Irandoc, and Magiran, too. We found many articles in this search. First, we selected 406 articles in all 6 search engines the relevant articles by a quick review of their titles and abstracts. Then, 178 related articles were selected based on their research subjects, i.e., ethical considerations in clinical trials and keywords use. However, 17 articles were duplicates, and the texts were not entirely related to their titles in 84 articles. Hence, they could not be used. Finally, after reading the full texts of the articles, 77 articles were selected to be evaluated (Figure 1).

Based on the articles' main themes, the clinical trials were divided into 4 parts: research design and question, approval and review of the designs, supervision and implementation stages, and publication of results. The related articles to each section were identified. It seemed that each stage could be divided into substages. For example, when it comes to the research question, it could be subdivided into "the equipoise" and the "design of research question" or "the instructions to write the question". In the end, 4 main stages and 9 substages were developed (Table 1). It should be noted that articles might be placed in one or more categories, according to the content and the issues in the study.

3. Results

A careful examination of the content of the articles revealed that "approval and review" and "supervision and implementation" had been discussed in 29 and 25 articles, respectively, and they had the most sensitivity among the authors. Then, "research question and equipoise" and "publication of results" with 17 and 13 articles, respectively, were in the lower ranks.

First, we reviewed the content of articles that generally discussed one or more of the above categories, except for the one listed in the title. According to Table 2, the issues of each substage in different articles were classified. In the stage of "approval and review", the most discussed topics were "approval by ethics committees and institu-

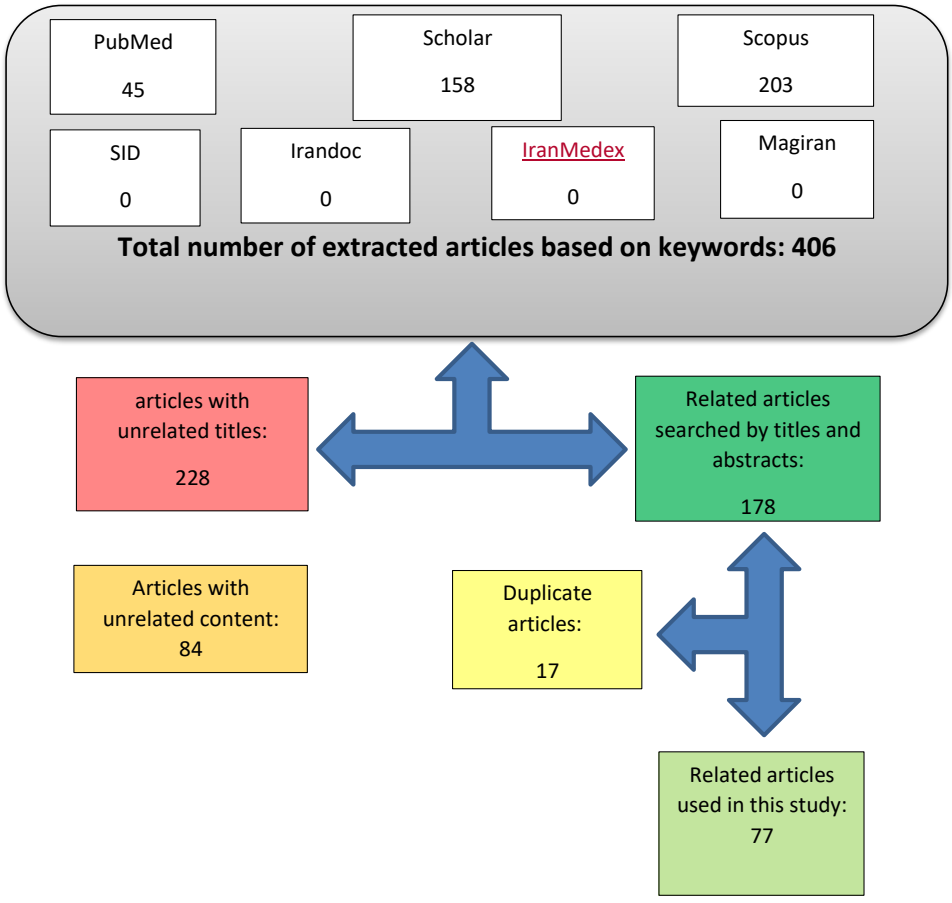

Figure 1. Searching based on resources

tional review boards", and "obtaining informed consent" mentioned in 18 and 14 articles, respectively. In the stage of "supervision and implementation", the substage of "supervision during implementation" was the most noticeable subject that 16 articles discussed. Subsequently, the "registry in the clinical trial registration platform"

Table 1. The areas under study to investigate the ethical challenges based on the subject

No.	Main Stage	Substage (s)
1	Research design and question	Question or Equipoise Design
2	Approval and review	Approval and supervision IRB and REC Informed consent
3	Supervision and implementation	Data collection Evaluating results Registry Oversight during implementation
4	Publishing the results	Publication

REC: Research Ethics Committees; IRB: Institutional Review Board.

Table 2. Frequency of articles (by subject) in journals based on 4 stages (n=84)

Web-Based Search Engines	Research Design and Question	Approval and Review	Supervision and Implementation	Publication of Results
Scholar	10	13	20	5
PubMed	2	10	4	7
Scopus	5	6	1	1
SID	0	0	0	0
Irandoc	0	0	0	0
Magiran	0	0	0	0
Total	17	29	25	13

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had been discussed in 9 articles, "data collection" in 5 articles, and "evaluation of results" in 2 articles.

The important note is that, as Table 3 shows, although the stages of "approval and review" and "supervision and implementation" are on top ranks (Table 2), by examining the content of the articles, it became clear that "research question" (27 articles), "designing the protocol" (22 articles) with totally 49 articles are still important issues to most authors.

Considering the ethical considerations, from the beginning of the research question to the publication of the results, and based on the stages of each clinical trial, we examined the essential points of each stage.

Research design and question

According to Benjamin Freedman's theory proposed in 1987 [2], studies discuss the principle of equipoise in the research question. Based on the definition of equipoise and the need to be indifferent to place each subject in the arms of the research, doubting the slightest therapeutic effect of a subject makes the assignment of patients to that intervention unethical. The researcher should have uncertainty about the therapy and study intervention. Another study [3] explicitly stated that attention to equipoise is not only an ethical principle for conducting research but also a major obligation for the researcher. Though in some cases the main objective is clear, the question proposed as equipoise may not be well-de-

Table 3. Frequency of subjects of the substages presented in Table 1 in the articles under study

Main Category	Title	PubMed	Scholar	Scopus	No.	Total
Research design and question	Question or equipoise	14	12	1	27	49
	Design	10	9	4	22	
Approval and review	Approval and supervision IRB and REC	4	9	5	18	32
	Informed consent	6	7	1	14	
Supervision and implementation	Data collection		5		5	32
	Evaluating the results	1	1		2	
	Registry	1	5	3	9	
	Supervision during implementation		8	8	16	
Publishing	Publication	7	6	2	15	15
Total		43	62	24	129	

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signed, which can reduce the validity of the research [4], or the title of the study may cause misconceptions about intervention or mislead the volunteers [5]. Sometimes there may be a difference between individual and clinical equipoise, which in the presence of clinical equipoise is a continuation of ethical research [3, 6] (Table 4). The authors have emphasized that each study should be designed to answer a specific question that responds to the needs of patients or the community or future problems and has appropriate and relevant scientific validity, and an independent review board can evaluate it if needed [7, 8]. It has also been emphasized that the research question must be carefully designed in relation to various studies with adaptive design.

Accordingly, the results can be interpreted [9-11] because the researcher can re-evaluate them based on the parameters obtained during the study [12]. Also, in pragmatic clinical trial studies performed in real environments, it is crucial to design research questions and topics. For instance, there is a possibility of obtaining informed consent and double risks in research or confirmation of the impact in real or controlled environments [13, 14]. The initial design of the research question and the protocol is essentially a principal document that must specify sufficient details to understand and implement the study properly [15, 16]. For example, a defective proposal may lead to a disaster, like studying drugs in London's Northwick Park Hospital [17]. Attention to determining the sample size and [18] personnel involved in the research and training methods of the people involved should also be carefully considered in the initial proposal and its design [19]. Obviously, in designing the research in exceptional cases such as small groups, e.g., in research on rare diseases or in a heterogeneous population, the issue should be accurately designed and implemented [20]. Because of insufficient budget, the research design must be done based on this restriction and even should be mentioned in the study [21]. Also, the compensation conditions and research insurance [22] and the role and presence of sponsors [23] must be mentioned (Table 4).

A study conducted in Germany and Turkey also examined major design issues such as the issue of consent and the problems of complementary medicine research [24, 25].

Considering issues such as DSMC (Data and Safety Monitoring Board) or interim analysis in the initial design is also an important point that can make the study more ethical and reliable in terms of ethics and standardization [26].

In general, it seems that the concern of equipoise research question and its precise design according to the type of clinical trial and research question has been one of the essential points of the authors.

Proposal review and approval

In this stage, the Institutional Review Board (IRB) and the Research Ethics Committee (REC) are primarily responsible for ethically reviewing proposals. What should be noted at first glance is the members' scientific competence and knowledge about relevant laws and regulations [27-29]. These committees are responsible for carefully reviewing the required ethics and standards before starting any clinical trial [30, 31]. In their reviews, the committees must carefully consider the necessary scientific issues and standards [32, 33] and examine the scientific competence, academic background, and relevance of the researcher's field of study and the subject of the clinical trial [33]. The committees are in charge of reviewing the details of the proposals in all parts, including financial issues, incentives to pay the volunteers, and sponsors, as well as planning to publish the results [21, 31, 34, 35].

Careful and comprehensive consideration of the proposals submitted to the committees, especially the study of the risks in the research, the conditions for obtaining informed consent forms, and the type of contract between researchers and volunteers, can be factors in establishing trust between researchers and patients or volunteers [36]. The committees are responsible for responding in due time to comment on the submitted research [37, 38].

The other issue that the committees should pay attention to is the requirement for guidelines and regulations related to complementary medicine and new technologies [39], which can be seen, for example, in the case of Iranian or Chinese medicine [40, 41] (Table 5).

Examining the content of the informed consent form in terms of honesty in expressing the subject, attention to vulnerable groups, the content, the literacy, and the language of the target groups should be carefully considered [42-44].

However, different articles have paid less attention to the appointment of an ethical supervisor and how to monitor the proper implementation of the plans according to the protocol and proposal approved.

Ensuring that the research is not started before obtaining the code of ethics is also one of the cases overlooked in these articles, indicating that either this issue is ac-

Table 4. Research question and equipoise/ Protocol design

Results	Authors	year	Journal	Type of Study	Title
The requirement to be fully indifferent to place each subject in the arms of the research	Bothwell & Kesselheim [9]	2017	The Hastings Center report	Review	The Real-World Ethics of Adaptive-Design Clinical Trials
	Chan et al. [15]	2013	Annals of internal medicine	Review	SPIRIT 2013 statement: defining standard protocol items for clinical trials
	Okonta [5]	2014	Niger Med J	Review	Ethics of clinical trials in Nigeria
Inappropriate design-misconceptions about intervention (therapy)	Okonta [5]	2014	Niger Med J	Review	Ethics of clinical trials in Nigeria
The requirement of clinical equipoise	Friedman et al. [4]	2010	Fundamentals of clinical trials: Springer	Review	What Is the Question? In: Friedman LMea, editor
	van der Graaf & van Delden [3]	2011	Clin Trials	Review	Equipoise should be amended, not abandoned
	Pallmann et al. [11]	2018	BMC medicine	Review	Adaptive designs in clinical trials: why use them, and how to run and report them
Consistency between the study and its background	Rosemann [12]	2019	Science as Culture	Review	Alter-Standardizing Clinical Trials: The Gold Standard in the Crossfire
	Hey &Truog [6]	2015	AMA journal of ethics	Case and commentary	The question of clinical equipoise and patients' best interests.
Scientific validity and response to needs	Pillamarapu, Mohan & Saberwal [7]	2019	Trials	Review	An analysis of deficiencies in the data of interventional drug trials registered with Clinical Trials Registry
	Mentz et al. [14]	2016	Circulation	Review	Good Clinical Practice Guidance and Pragmatic Clinical Trials: Balancing the Best of Both Worlds
Designing the protocol with sufficient details about sample size, time, involved personnel, insurance, small groups, interim analysis, and DSMC	Chan et al. [15]	2013	Annals of internal medicine	Review	SPIRIT 2013 statement: defining standard protocol items for clinical trials
	Sajdak, Trembath, Thomas [19]	2013	Journal of nuclear medicine technology	Review	The importance of standard operating procedures in clinical trials
	Day et al. [20]	2018	Orphanet journal of rare diseases	Review	Recommendations for the design of small population clinical trials
	Jesani & Amar [22]	2019	Indian Journal of Medical ethics	Review	New Drugs and Clinical Trials Rules, 2019: The market trumps ethics and participant rights

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cepted as a principle in developed countries and there is no violation in this regard or the authors' sensitivity in this regard is not as much as the other issues raised in articles under review (Table 5).

In general, the greatest emphasis of the authors in the "approval and review" stage is on the scientific competence of the members of the ethics committees and their familiarity with the rules and regulations, which significantly helps to judge projects and design protocols better and eliminate their shortcomings.

At the same time, the issue of how to obtain informed consent from the volunteers has also been considered.

Supervision and implementation

At this stage, the articles have emphasized registering a clinical trial in the relevant systems and observers' access. Registration of research projects in the International Clinical Trials Registry Platform (ICTRP) has increased about 5 times from 2004 to 2013 and has become an essential factor of transparency in clinical trial research [45, 46]. The registration not only indicates the

number of clinical trial studies by providing access to monitoring committees but also provides the possibilities of reviewing the registration conditions and process as well as the content of the approved protocol to comply with what was submitted to the committees to follow any non-compliance. Furthermore, the registration allows for more protection of and faster access to data and monitoring the implementation of the project in accordance with the approved protocol and reviewing the results by journals to verify them and apply research codes, such as SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) and CONSORT (Consolidated Standards of Monitor Reporting Trials) [45, 47]. It can also allow the committees to be informed of the starting time of the trials and prevent ethical violations or retrospective trials from achieving a specific result [46, 48], as the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) have considered registration in the registry platform before conducting any research as an essential principle [46]. A study found that one-fourth of studies in 2013 started recruiting the volunteers before registering in the platform, and they were, in fact retrospectively registered, which undermines trust in the results [45]. In a study in Iran, it was found that 86.1% of clinical trials have been registered in the clinical trial registry platform after the recruitment of volunteers [49].

Registration of projects in the registry platform and sharing the research data in this system are essential factors for transparency and help proper monitoring and researcher's adherence to the approved protocol [8, 47, 50]. This procedure may help resolve challenges in access to data quality, increase access to protocols and data results, make it easier to search for clinical trials, increase trust in medical research, reduce design errors and publish results, and avoid serious risks [45, 51].

The rules for registering clinical trials in different countries have already been developed. For example, in England, a research project must be registered in the system up to 6 weeks after the starting time of the study [52, 53]. However, in England, despite all provisions, one-fifth of the trials are not registered in the system [52]. Similarly, the same rate was seen in China, with about 65% incomplete registration in 2009 [54].

Collecting and recording the data obtained from the research, ensuring the accuracy of data, determining the methods of data collection and their validation are important parts of monitoring and implementation [14, 45]. Missing data is another factor that should be considered while implementing a project. Moreover, the factors causing missing data, especially the withdrawal of the subjects from the research, should be appropriately recognized, and the condition to prevent it should be considered, which is generally to pay attention to obtaining informed consent and providing the research subjects with sufficient information [55].

How committees or ethical supervisors oversee the proper implementation of the proposed protocol is also essential. Such monitoring should be done at all stages, the most important of which is how to call volunteers and how to obtain informed consent forms, the stability, and continuity of monitoring, preventing its distortion or elimination [56]. However, it seems that there is no written or unified method or instruction in this field, and it is suggested to use valid evaluation checklists [39, 57]. The possibility of supervisors' access to what is registered in the registry system by the researcher is a factor for better verification and monitoring of the trials' conductance. And recording the ethical considerations provided by the ethics committees in the system makes it possible to follow the researcher's commitment to observing them [51].

Using items such as Interim Analysis or DSMC (Data and Safety Monitoring Board) can be very effective in monitoring the implementation of any research, reducing human and financial costs, and contributing to research ethics [8, 58-61].

In summary, in the monitoring and implementation stage, the issues of collecting data and monitoring are the most sensitive matter among authors.

Also, issues such as registering in the relevant systems and starting after receiving the code of ethics have received serious attention.

Publication of the results

Publication of research results is an essential part of science development and sharing the results of studies, which unfortunately is sometimes ignored for some reasons, and the results are not appropriately published or not published at all. A study reported that only 68% of registered prospective studies had posted the results [62]. In a study in 2019 on 5 valid medical journals, it was revealed that only 76.3% of projects published the initial results. However, there are regulations to publish the results following CONSORT and SPIRIT [63]. In a systematic review study in 2017 on top 50 medical journals, it was found that 14 trials (out of 927 clinical trials) failed to fully publish the missing codes of conduct and about 63% of the required components [31]. This

Table 5. Proposal review in the committees

Title	Type of Study	Journal	Year	Authors	Results
Ethics committee: Critical issues and challenges	Review	Indian J Pharmacol	2012	Desai [27]	Scientific competence and knowledge of the members of these committees about the relevant laws and regulations
Ethics Committees in India: Past, present and future	Review	Perspect Clin Res	2017	Thatte & Marathe [28]	
The Function of Medical Ethics Professionals in Ethical Review of Clinical Trials Involving Human Subjects	Review	Chinese Medical Ethics	2016	Liu & Xinying [29]	
Global clinical trials: ethics, harmonization and commitments to transparency	Review	Global Health	2015	Li et al. [31]	Scientific review of the proposal and compliance with the standards
A systematic review finds underreporting of ethics approval, informed consent, and incentives in clinical trials	Systematic review	Journal of Clinical Epidemiology	2017	Trung et al. [30]	
Statistical power, the Belmont report, and the ethics of clinical trials	Review	Science and engineering ethics	2010	Vollmer & Howard [32]	Examining the researcher's scientific and academic competence
Comparative effectiveness research: What to do when experts disagree about risks	Review	BMC Med Ethics	2017	Lie etal. [33]	
Resource use, costs, and approval times for planning and preparing a randomized clinical trial before and after the implementation of the new Swiss human research legislation	STROBE	Trials	2019	Speich, Schur, Gryaznov [37]	Requirement to respond in due time to comment
A systematic review finds underreporting of ethics approval, informed consent, and incentives in clinical trials	Systematic review	Journal of Clinical Epidemiology	2017	Trung et al. [30]	Examining the details of the proposals in all parts, such as financial issues, incentives to pay the volunteers, and sponsors, and even planning to publish the results, and especially examining the risks in the research, the conditions for obtaining informed consent and the type of contract between researchers and volunteers
Guidance on clinical research involving infants, children and young people: An update for researchers and research ethics committees	Review	Archives of Disease in Childhood	2014	Modi et al. [34]	
Tracking the timely dissemination of clinical studies. Characteristics and impact of 10 tracking variables	Explorative follow-up study	F1000Research	2018	Strech et al. [35]	
When is it rational to participate in a clinical trial? A game theory approach incorporating trust, regret and guilt	Review	BMC medical research methodology	2012	Djulbegovic & Hozo [36]	
Ethics Committees in India: Past, present and future	Review	Perspect Clin Res	2017	Thatte & Marathe [28]	The need for instructions and regulations related to complementary medicine and new technologies
The Challenges of Clinical Researches in Iranian Traditional Medicine (ITM)	qualitative	Iranian journal of medical sciences	2016	Tabarrai, Qaraaty & Aliasl [39]	
Chinese ethics review system and chinese medicine ethical review: Past, present, and future	Review	. Chinese Journal of Integrative Medicine	2011	Li, Du, Ji, Wang [40]	
The ethics of clinical trials	Review	Ecancermedicalscience	2014	Nardini [26]	Examining how the informed consent forms were obtained, as well as their content in terms of therapeutic misconceptions, unrealistic hopes, failure to include research title
Ethical considerations in placebo-controlled randomised clinical trials	Review	BJPsych open	2015	Kaufman [40]	
Research involving adults lacking capacity to consent: the impact of research regulation on 'evidence biased' medicine	Review	BMC Med Ethics	2016	Shepherd [42]	
Ethics in clinical research in India: A survey of clinical research professionals' perceptions	Cross sectional	Perspect Clin Res	2013	Jadhav & Bhatt [43]	
Readability of informed consent forms in clinical trials conducted in a skin research center	Cross sectional	J Med Ethics Hist Med	2016	Samadi & Asghari [44]	

finding is in line with the results of other studies [14]. Ethical supervision of a clinical trial should be ongoing from the start, and the results should be registered in the registry system until publication. In the recent revision of the Declaration of Helsinki, all committees have such a right [64]. The editors of the journals must require the authors to provide the link of registration when they plan to publish the results [65]. This requirement may be suggested due to problems, such as publication bias and reporting bias that occur when the outcome of an experiment or research study influences the decision of whether to publish or distribute it [66]. In the European Union, the requirement to provide a summary of the results of clinical trials by the sponsor to the European Database was approved in 2014. However, a report states that only 13% of eligible trials have submitted this report to clinicalTrial.gov [64]. The publication of results and the obligation to share them as a moral duty is also recommended by the International Committee of Medical Journals Editors (ICMJE) to respect the individuals who put themselves at risk [66]. Another important issue in publishing the results, which is ethically of great importance, is plagiarism that can be reduced by training and practical use of appropriate software with text [67]. The authors should pay more attention to publishing all the results (whether positive or negative) at this stage and emphasize transparency in publishing the results.

Ethical considerations in Iran

The initial regulations of ethics committees in the Iranian medical sciences research were adopted in 1999 and revised twice in 2004 [68] and 2013. In this instruction, based on the Declaration of Helsinki and codes of conduct in global research and the national cultural and religious values, essential issues such as protecting the research subjects and their rights have been addressed. This document was prepared in 31 paragraphs.

In 2003, simultaneous with the proposal of the World Health Organization to the Ministry of Health of Iran to join the Good Clinical Practice Program (GCP), a clinical studies committee was formed as a specialized committee at the Food and Drug Administration. In 2007, it was renamed the Department of Clinical Studies and Care. By compiling strict supervisory regulations, it standardizes and closely supervises the conduct of clinical trials, especially clinical trials with industrial sponsorship. One of these guidelines is the "general guide to ethics in medical sciences research with human subjects in the Islamic Republic of Iran". This guideline explains the basic and binding principles of research with human subjects in 31 sections, which is mainly based on the Declaration of Helsinki and also the "Ethical Guide to Clinical Trials in the Islamic Republic of Iran". It has three chapters of the ethical issues related to clinical trials in the topics of "profit and loss assessment", the second chapter "conscious satisfaction", and the third chapter to "placebo". In 2014, the Deputy Minister of Research and Technology of the Ministry of Health and Medical Education emphasized the requirement to register a clinical trial in the system of the Iranian Clinical Trial Registration Platform (www.irct.ir) based on the guidelines of the World Health Organization (www.who.int.ictrp). In 2017, the Minister of Health of the Islamic Republic of Iran announced the procedure for investigating research violations in a regulation that has mentioned issues, such as failure to register a clinical trial in the registration system, failure to get a code of conduct, failure to comply with ethical standards in publishing results, failure to respect confidentiality and obtaining informed consent, and data distortion or plagiarism as examples of misconduct.

The draft of ethical guidelines to publish research results was first compiled in Iran in 2009 and revised in 2017, in which the ethics in publishing research results are discussed in detail.

However, none of the regulations and guidelines presents any specific and clearly defined issues about research question and equipoise. There is also insufficient reference or accuracy in the design of clinical trial protocols, especially in cases such as interim analysis or Data and Safety Monitoring Board (DSMB). Also, no comprehensive guidelines or regulations show how to implement a clinical trial.

Though there are clear guidelines and regulations in many cases, there is not enough information about adherence to them in national clinical trials. In the present review, we only found 4 articles in the field of clinical trials with the mentioned issues. Two articles were related to the evaluation of obtaining informed consent and its understanding by the people and the role of the ethics committees [69, 70]. Ghasemzadeh et al. [70] reviewed all clinical trials approved by the Research Ethics Committee of Tehran University of Medical Sciences (TUMS) conducted in 2007 and found that in only 66.7% of the studies, the objectives of the tests were explained in informed consent and in 38.6% of studies with informed consent, it was mentioned that participation is voluntary. In 2016, it was found in a study on informed consent forms of a clinical trial that these forms are very complex and not understood by the public. The present study results revealed the need for ethics committees

Table 6. Supervision and implementation

Title	Type of Study	Journal	Year	Authors	Results
Trends in global clinical trial registration: an analysis of numbers of registered clinical trials in different parts of the world from 2004 to 2013	Cross-sectional	BMJ open	2015	Viergever & Li [45]	Registering clinical trials for faster access to data and monitoring the implementation of the projects according to the approved protocol, non-registration of retrospective studies,
The quality of registration of clinical trials	Cross-sectional	PlOS One	2011	Viergever & Ghersi [46]	
Can research ethics committees enable clinical trial data sharing?	Review	Ethics, Medicine and Public Health	2017	Thorogood &, Knoppers [47]	
Public titles of clinical trials should have ethics review	Review	J Clinical Epidemiol-ogy	2015	Saenz et al. [48]	
Characteristics of Clinical Trials in Iran: A Sample of 5000 Trials Registered in Iranian Registry of Clinical Trials (IRCT)	Cross-sectional	Iranian Journal of Epidemiol-ogy	2019	Fakhri et al. [49]	
Systematic evaluation of the patient-reported outcome (PRO) content of clinical trial protocols	Systematic review	PlOS One	2014	Kyte et al. [16]	Collecting and register-ing the data obtained from the research, ensuring the accuracy of data, determining the data collection
Trends in global clinical trial registration: an analysis of numbers of registered clinical trials in different parts of the world from 2004 to 2013	Cross-sectional	BMJ open	2015	Viergever &, Li [45]	
Why we need easy access to all data from all clini-cal trials and how to accomplish it	Review	Trials	2011	Gøtzsche [50]	Missing data, identify-ing the risk factors for missing data
Ethics committees in India: past, present, and future	Review	Perspect Clin Res	2017	Thatte & Marathe [28]	How the committees and ethical supervisors monitor the proper implementation of research in accordance with the plan provided
Making a decision about trial participation: the feasibility of measuring deliberation during the informed consent process for clinical trials	Cross-sectional	Trials	2014	Gillies et al. [55]	
Randomized evaluation of government health programs does present a challenge to standard research ethics frameworks	Review	Journal of Medical Ethics	2020	Watson et al. [56]	
Quantitative Framework for Retrospective Assess-ment of Interim Decisions in Clinical Trials	Review	Medical Decision Making	2016	Stanev [57]	Using items such as interim analysis or DSMC (Data and Safety Monitoring Board)
Information time scales for interim analyses of randomized clinical trials	Review	Clinical Trials	2016	Freidlin et al. [60]	

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to pay attention to the ability to read informed consent forms prepared by various research centers [44].

Ghasemzade et al. [70] examined the research projects approved by Urmia University of Medical Sciences from 2003 to 2008. They found that only 37 clinical trials (out of 60) (62%) were referred to and approved by the ethics committees. Only 85.5% of the studies completed the ethical considerations section.

The fourth article was conducted in 2016 on clinical trials in traditional medicine and problems, including research design, data collection, and then posting the results [40].

4. Discussion and Conclusion

The review of articles published between 2010 and the end of 2019 on the ethical, technical considerations, and standards of conducting clinical trials showed significant progress in conducting and monitoring clinical trials. However, despite the relevant laws, instructions and regulations, there are still concerns about the gap between what is done and what should be done. Bridging these scientific and practical gaps requires a comprehensive effort by all stakeholders.

According to the published articles, the important concerns rest on the stage of proposal review and approval of clinical trial protocols and the important and effective role of these committees, especially the discussion of competence and knowledge of the committee members, as well as re-

Table 7. Publishing the results

Title	Type of Study	Journal	Year	Authors	Results
Tracking the timely dissemination of clinical studies. Characteristics and impact of 10 tracking variables	Explorative follow-up study	F1000Research	2018	Strech et al. [35]	Failure to publish the results in 68% of cases
Systematic evaluation of the patient-reported outcome (PRO) content of clinical trial protocols	Systematic review	PlOS One	2014	Kyte et al. [16]	Failure to fully publish Ethical codes
A systematic review finds underreporting of ethics approval, informed consent, and incentives in clinical trials	Systematic review	Journal of Clinical Epidemiology	2017	Trung et al. [30]	
The contribution and attitudes of research ethics committees to complete registration and non-selective reporting of clinical trials: A European survey	Case series	Research Ethics	2016	Strech & Littmann [65]	The ability to access the registration system to verify and match the results with the approved protocol
The ethics of reporting all the results of clinical trials	Review	British medical bulletin	2017	Brassington [66]	
Interventions to prevent misconduct and promote integrity in research and publication	Review	Cochrane Database Syst Rev	2016	Marusic et al. [67]	Examining whether plagiarism occurred

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viewing the protocol and obtaining informed consent from the candidates. The proposal review and approval stage is when the submitted proposal is not carefully considered in the following stages, and especially in the implementation stage, that may lead to various abuses and problems.

Another serious issue was the supervision and implementation of clinical trials and adherence to the declared protocols, and checking the degree of compliance and adherence. The presence of an observer for the projects and how they are supervised is also essential and noteworthy.

How to obtain informed consent (which, unfortunately in some countries, informed consent is not yet fully and completely obtained), data collection, protection, and prevention of data bias and prejudice are also considered.

The essential issues in the first steps of all actions that articles and authors have much considered are choosing a research question, designing an appropriate protocol with that question, and adapting the study to the context of doing it. It seems that special attention has been paid to the research question and equipoise and in the future, more attention will be paid to it. In publishing the results of clinical trials, failure to publish the results at all or publication of defective and biased results and research to verify the results were the most important issues mentioned in the articles.

There are some questions and points that were ignored in these articles. According to the ICTRP Global System, the registry of clinical trials has increased about fivefold from 2004 to 2013 [45]. Does this mean that research questions and vague scientific points or unknown topics in medical sciences have increased 5 times in this period, or the thirst for research has increased among researchers? This lack of attention to the criteria for selecting a research question in terms of applicability and its benefits for science and human societies, in addition to the ethical challenge of such clinical trials, can also be considered in terms of allocating resources for clinical trials.

The criteria of the ethical supervisor and how to determine the ethical standards of the plans and conditions and the method of monitoring the good conduct of clinical trials in accordance with the proposed proposal are not clearly defined. In case of changes in the approved protocol, the supervisor's access to the trial and compliance with the original version, the access to the registration system, examining any deviation from the approved and running protocols are the issues that should be carefully considered.

The next note is defining the ultimate advantage of accurate implementation of the research under the declared and approved protocol for the researcher. Is there an advantage for the researcher in ethical evaluations in case of full compliance with the protocol and ethical and professional standards? Will such adherence to standards have an advantage for the researcher in the future? How about the ethical supervisor? Does more comprehensive and more accurate monitoring have advantages for the researcher? Or is it enough that the researcher must be professional and adhere to observe standards and regulations?

Ethical Considerations

Compliance with ethical guidelines

This article is a review article with no human or animal sample.

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Author's contributions

Conceptualization and supervision: Shahriar Moosavinejad, Mehrzad Kiani; Investigation, writing – original draft, and writing – review & editing: All authors.

Conflict of interest

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