A narrative review on the development of the ethical review mode of multicenter clinical trials in China

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Background and Objective: The number of new drug clinical trials in China is surging, and ethics review played an important part in clinical trials. However, there are certain problems of ethical review in China. This review aims to conduct a review to propose recommendations of an ethical review mode for multicenter clinical trials and ultimately contribute to improving the ethics review mechanism and the efficiency.

Methods: A literature review, publication research and interpretation of the related governmental policies and requirements in China were conducted to collect available information for analysis of the current situation in terms of the various ethical review modes for multicenter clinical research. The literatures and information were searched and selected from national and international database and related governance website by following some inclusion and exclusion criteria. And a comparation with the relevant practical experience in the USA was conducted to support the proposing of recommendations to China by referring to some successful practice in the USA.

Key Content and Findings: China has undergone several stages of development. The most traditional and least efficient model is institutional review boards (IRBs) review, which is most commonly used. After IRB review mode, other modes such as central IRB and single IRB review have emerged, which have improved the efficiency of ethical review. However, multiple challenges exist like, no clear definition of regulatory responsibilities and the consensus is not easy to be made due to the gap of interpretation and the unbalanced development on ethic review system from Chinese hospitals.

Conclusions: The multicenter ethical review should adopt the conditional 'approval' mode of the leading site's ethical review decisions, gradually establish a single IRB review and select the best ethics committee. Regional ethics committees can gradually take responsibility for the primary review in the multicenter ethics review model and ultimately contribute to improving the mechanism and efficiency of the ethics review.

Keywords: Cooperative review; ethics review; institutional review boards (IRBs); multicenter clinical trials

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Introduction

The ethical review of multicenter clinical trials is to review the information about the physicians, scientists, and community members involved in the research. It's a hot issue globally and a common concern for all parties involved in clinical research, including governments, sponsors, research institutions, investigators and ethics committees. As an important part of the clinical trials of new drugs, the ethics review, regardless of its mode and method, should not only improve efficiency but also ensure the quality and scientific reliability of the study and guarantee the rights and safety of the subjects, in addition to guidelines that need to be followed as proposed by Good Clinical Practice (GCP).

Institutional review boards (IRBs) are an important part of regulatory efforts. An IRB is an ethics review committee that is in place to ensure human research subjects' rights are protected when involving into a clinical trial study. The responsibility of IRB is also to protect the rights of the patients to ensure they can ultimately gain benefit from the trial. A typical IRB is composed of physicians, a scientist, a non-scientist, and a representative from the community from which the human subjects are drawn. Before conducting a clinical trial or implementing amendments, etc., the IRB's approval is mandatorily required. How scientifically and efficiently the ethic review conducted by IRB will influence the judgement of the scientific of clinical trials, whether an appropriate balance of risks and benefits can be made for the human being participates and the efficiency of clinical trials execution,

However, China is still developing models of multicenter clinical trial ethics review, and different Chinese hospitals sometimes are implementing different ethics review models which may cause the low efficiency of multicenter clinical trials conduction. As traditional and publicly used models, IRB review, centralized ethics review and single IRB review are all implemented in Chinese hospitals. Recently some new ethic review models like regional ethics committee (REC) and collaborative ethics review consortium have also been proposed and established in part of hospitals in some Chinese provinces.

We investigated both the development of multicenter clinical trial ethics review models in China and found there are some existing problems in the different modes of development, adaptation, and implementation. There is no clear and standard criteria of different ethics review modes execution in China, in the meanwhile the consensus in Chinese hospitals is not easy to be made due to the gap of interpretation and the unbalanced development on ethic review system from different Chinese hospitals.

Recently, China issued some new policies and regulations in terms of ethic review of clinical trials, and the efficiency of multicenter clinical trials execution is necessarily to be improved. It's meaningful to propose recommendations regarding the establishment and implementation of an ethical review mode for multicenter clinical trials in China. However, there is very limited comprehensive review on the ethical review mode in China. Based on a narrative review of current development status of ethic review modes and research of the existing problems, this article aims to provide some thoughts and suggestions on how to implement multicenter clinical trial ethics reviews under the new policies and regulations in China. We present the following article in accordance with the Narrative Review reporting Checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5213/rc).

Methods

The goal of this review was to describe the status of the ethics review mode development for multicenter clinical trials in China. In the preliminary literature review, we mainly identified articles from national and international database by searching a variety of keywords, including "single IRB", "centralized IRB", "cooperative review" and "regional IRB". A detailed search strategy summary is shown in *Table 1*.

In addition, we interpreted the related governmental policies and requirements of the Chinese Food and Drug Administration (FDA) by consulting and referring to the opinions of Chinese experts on IRBs. In the literature research period, we referred to the data and information provided by the article authors, for majority of them are front-line IRB managers and related affiliations. As necessary, some consultant to front-line IRB managers and Chinese experts were made by our authors to exchange the opinions and insights on the current situation in terms of the various ethical review modes for multicenter clinical trials in China, what's the existing problem and main challenges when establishing and implementing these ethical review modes in their hospital institute or from governance supervision perspective. In the meanwhile, we compared these modes with the relevant practical experience in other developed countries, such as the USA as well. Such comparation with the relevant practical

Table 1 The search strategy summary

Items	Specification
Date of search	From 1-Nov-2021 to 30-Sep-2022
Databases and other sources searched	CNKI (https://www.cnki.net/)
	Wanfang Database (https://www.wanfangdata.com.cn/)
	CQVIP Database (http://www.cqvip.com/)
	Springer (www.link.springer.com)
	ScienceDirect (https://www.sciencedirect.com/)
	PubMed (https://pubmed.ncbi.nlm.nih.gov/)
Search terms used	Clinical trials, clinical research, multicenter clinical trials, IRBs, ethic review, central IRB review, cooperative review
	Note: a detailed search strategy of CNKI database as an example is shown in Table S1
Timeframe	From Jan-2007 to 2022 up to date
Inclusion and exclusion criteria	Inclusion:
	Study type: review or original research article
	Language: English (for international database) or Chinese (for national database)
	Exclusion:
	Study type: dissertation, meeting, newspaper, book, patent, annual, industry standards
Selection process	The searching in database, the selection of literature and the collection and assembly of data were conducted author Jing Ding, Yashu Yin and Keke Fang. The data analysis and interpretation were conducted by author Jing Ding, Yashu Yin and Keke Fang as well. All authors reviewed the literatures and draft manuscript together, revise subsequentially until obtaining a consensus on the comments
Any additional considerations, if applicable	For some opinions proposed by the authors from one particular article which couldn't been successful searched through reference link, will be excluded from data assembly

IRBs, institutional review boards.

experience in the USA was to support the proposing of recommendations by referring to some success practice in the USA.

Key content and findings

China has undergone several stages of development ranging from institutional ethics committee review to central ethics review and single ethics review/ethics review mutual recognition, and the exploration of the ethics review system has been gradually clarified. However, there are multiple challenges during the establishment and implementation of each ethical review mode for multicenter clinical trials in China.

IRB review

An IRB review means that a participating site of a multicenter clinical trial does not accept the ethical review decision of the leading site and conducts a meeting review or expedited review of the project according to the risk of the trial, including the scientific and ethical rationality of the trial protocol, the feasibility of the trial in the institution, the localization of informed consent, and various types of follow-up reviews after the clinical trial is conducted. This ethical review model is the most common one in the conduct of multicenter clinical trials in China. In a related survey in 2009, 65.1% of survey respondents indicated that their institution did not currently accept the

leading site's ethics review and that ethics reviews must be conducted independently for multicenter clinical trial projects carried out at their institution regardless of the outcome of the review by the leading site (1).

The main reason for not accepting the ethical review results of the leading site in a multicenter clinical trial is concerns over the quality of those ethical reviews. In the case of the quality of the review by the leading site not being able to be assessed, the ethics committee of the participating site conducts another thorough and detailed review of the trial project based on its own responsibility. On the one hand, the participating site can play a positive role in ensuring the safety and rights of the subjects in the institution; however, on the other hand, if each institution proposes different opinions for modifying the trial protocol, doing so brings great challenges to the sponsors when coordinating a clinical trial. At the same time, multiple ethics reviews lead to unnecessary duplication of reviews in some aspects, making the ethics review process long and inefficient. A study has shown that the percentage of issues raised by repeat reviews that are very important from the perspective of subject protection is very small, so repeat reviews are not very meaningful (2).

Based on this, to facilitate the transformation of new drugs, on December 1, 2019, the new *Drug Administration Law of the People's Republic of China* was officially implemented and changed drug clinical trials from following the 'approval system' to the 'implied licensing system'. This amendment allows the ethical reviews to be conducted simultaneously with the approval of clinical trial applications, referred to as the 'Ethical Pre-Review'. The ethics committee starts the ethical review without obtaining the "*Notice of Drug Clinical Trial or Implied Public Notice from the Center for Drug Evaluation (CDE) of National Medical Products Administration (NMPA)*". This increases the review of nonclinical study data and the consideration of the rationality of the protocol design so that the key points of the ethical review are more focused on the risks and benefits faced by the subjects, and an ethical approval letter can usually be obtained after obtaining the clinical trial approval letter. This process has greatly improved the efficiency of clinical trials prior to initiation and has played an important role in accelerating the launch of new drugs. Currently, according to Clindata statistics, as of September 2019, there are more than 60 hospitals in China, including the authors' institution, accepting the 'Ethical Pre-Review', and the trend is increasing year by year. In addition, for multicenter clinical trials, the majority of leading sites accept the 'Ethical Pre-Review', and for participating sites that allow the 'Ethical Pre-Review', eliminating the need to wait for the results of the ethical review by the leading site before starting their own review or granting ethical approval letters is also key to the efficiency of trial initiation.

Centralized ethics review

The concept of a centralized ethics review was introduced in the 2006 guidance, "*Using a Centralized IRB Review Process in Multicenter Clinical Trials*", issued jointly by the U.S. Department of Health and Human Services and the FDA (3). The adoption of a centralized ethics review model aims to prevent sponsors from seeking ethics committees that have insufficient review capacity and are more likely to pass on the project (i.e., preventing the phenomenon of so-called IRB shopping). At the same time, the adoption of a centralized ethics review model for multicenter clinical trials can better improve the efficiency of the review. The central IRB is responsible for all reviews: from initial review to the end of the study, including review of the scientific and ethical issues of the protocol and the informed consent. The participating site accepts the opinion of the central ethics review and archives all clinical trial documents without conducting a separate meeting review or expedited review.

This alternative review model reduces unnecessary duplication of reviews, shortens the time frame for the ethical review of multicenter clinical trials, and facilitates the coordination and management of multicenter clinical trials by sponsors, but it is not commonly conducted in China (1). Huang *et al.* reported that only 34.9% of institutions accepted centralized reviews, and 65.1% of institutions did not accept centralized reviews (1). Some universities, research institutes and other research institutions that do not have ethics committees may accept this form of centralized review when they participate in multicenter trial projects. However, most of the institutions participating in drug clinical trials generally do not accept the centralized review, mainly for the following reasons. (I) Unclear definition of regulatory responsibilities. There is no regulation that specifies the responsibility of the central IRB or of the participating IRB. In the central ethics review model, the central IRB assumes all reviews from the beginning to the end of the trial. However, if there is no provision for responsibility, will the central IRB only review what happens within its own center and not review the aspects related to the participating sites? Will the participating IRBs themselves stop focusing on the risks

of the trial and the safety of the subjects in their own sites because the central IRB is the only IRB in this model? (II) At present, the level of development of ethics committees in China varies, and participating sites are concerned about the ability of the central IRB to review, fearing that they will not be able to express an opinion if the central IRB makes a review error. (III) The working process of each institution's ethics committee is inconsistent, and accepting a centralized review means the need to adjust its own forms and standard operating procedures (SOPs) to accommodate the central IRB's review, especially for institutions that use an electronic management system. When the management system cannot meet the needs of the central IRB's process, the work will become very complicated or even impossible to complete. (IV) Participating IRBs also have other concerns, such as the fear of losing benefits (e.g., funding for the review) and the possibility that the informed consent form reviewed by the central IRB might not be adapted to the local situation (4).

Single IRB review

The concept of a single IRB review first appeared in the 2011 revision of the U.S. *Federal Common Rule for the Protection of Subjects*. A single IRB review is not about choosing an IRB to replace others but, instead, through self-nomination or a recommendation within the peer group, a reviewing IRB is selected that is primarily responsible for reviewing the scientific and ethical rationality of the protocol, and other participating sites rely on this IRB, accept its opinion and no longer repeat the review. As the first step of the single IRB review system, the most suitable ethics committee is identified and select as the reviewing IRB without the need to confirm the acceptability by each ethics committee after the review; therefore, the process improves the review's efficiency and reduces the burden on investigators.

The single IRB review is a collaborative review system was first proposed in China in 2010 when the NMPA issued the *Guidelines for Ethical Review of Drug Clinical Trials* (herein the Guidelines), which states that "*collaborative review procedures may be established for multicenter clinical trials*: *the leading site's ethics committee is responsible for reviewing the scientific and ethical rationality of the trial protocol (5)*. *The ethics committee of each participating site is responsible for reviewing the feasibility of the trial at their sites subject to the review opinion of the ethics committee of the leading site*". However, the earliest explicit introduction of the concept of a single IRB was in the revised draft, *Ethical Review Approach for Biomedical Research Involving Humans*, promulgated by the National Health Commission of the People's Republic of China on May 4, 2018: "*Multicenter clinical trial research is subject to a single IRB review*, *and the ethics committee that undertakes the single review is responsible for the scientific nature of the biomedical research protocol*, *the protection of the legitimate rights and interests of the subjects and the promotion of the standard conduct of biomedical research*".

Although the drug regulatory authorities and the Health Commission have provided guidance on collaborative reviews, this model has not been conducted well in China for the following reasons. (I) Although the Guidelines propose the collaborative review as a working model, they do not give clear guidance on how to establish a collaborative review working system. Does a collaborative review, or ethical mutual recognition, require a prior agreement? How is the reviewing IRB to be nominated? etc. (II) Multicenter clinical trials often span multiple provinces and involve various types of medical institutions at all levels, and the situation is very complex. Without national-level policies and regulations to clearly define the responsibilities of the leading and participating sites, it is difficult for the collaborative review system to get off the ground. Although the Health Commission's guidelines may address issues that span provinces and geographic areas, the document is still in the phase of seeking comments. On the other hand, multicenter clinical trials of drugs and medical devices for registration purposes need to meet not only the regulations of the Health Commission but also those of the drug regulatory authorities. The single IRB model is only mentioned in the Health Commission's Guidance, which is not mandatory; therefore, many institutions do not accept the single IRB model. (III) Multicenter clinical trials usually consider the site of the leading principal investigator (PI) as the leading site. Although the leading PI represents the leading academic level, the ethics committee of the PI's institution does not necessarily have a matching level. Some leading sites' ethics committees have less frequent meetings and low review efficiency, and sometimes the quality of a review is not guaranteed, which makes the collaborative review model not well implemented. In view of the importance of the authority of a single IRB, it is recommended that a single IRB should be not only the leading site's IRB but also that of an REC, professional ethics committee or research institution's ethics committee, with a strong review capability and selected through consultation and delegation.

Regional ethics committee

To improve the mechanism of China's ethics committees and improve the low quality development of China's pharmaceutical industry, the General Office of the State Council and the General Office of the Central Government jointly issued the *Opinions on Deepening the Reform of the Review and Approval System to Encourage Drug and Medical Device Innovation* (herein the Opinions) on October 8, 2017, which clearly stated specific measures to improve the efficiency and quality of ethics committee reviews, including "*Localities may establish RECs as needed to guide the ethical review of clinical trials and may accept commissions from institutions or registration applicants that do not have the conditions to conduct ethical reviews to conduct an ethical review of clinical trial protocols and supervise the conduct of clinical trials*". This is the first time that a clear definition was provided for the role of the REC to accept the commission to conduct a review and do a good job of monitoring the conduct of a trial. RECs are usually initiated by local health administration authorities, built by relevant units (local pharmacy societies, clinical research centers, etc.), and composed of experienced ethics review experts from local institutions. RECs are responsible for providing training to local institutions, assisting in the construction of local institutional ethics committees, providing advice on difficult ethical issues, and accepting delegated reviews. Because the members of RECs cover relevant medical institutions, universities and other research organizations in the region or specialized field, the RECs can, to a certain extent, solve the problem of a collaborative review as mentioned in the Guideline of the NMPA, the Draft for Public Comments of the Health Commission and the Opinions of the two state offices of China.

In China, the Sichuan Regional Ethical Review Committee for Traditional Chinese Medicine (Sichuan TCM REC) was established in Chengdu in April 2012 as the first REC, which started the exploration of REC construction. Subsequently, RECs have been established in Shenzhen, Shandong, Shanghai, Guangdong, Beijing, Jiangxi and Nanjing. All of these RECs have publicly stated that their main responsibilities are to provide training and consultation, establish ethical review norms in the region and undertake delegated reviews. However, these same RECs vary greatly in their undertaking of ethical reviews. Among them, the one that has undertaken the largest number of projects is the Sichuan TCM REC. As of October 2018, 460 biomedical studies involving human subjects have been reviewed (including 263 scientific research projects), which is the highest number of projects reviewed among the RECs with published data (6). Fewer reviews have been undertaken by other RECs, mainly for the following reasons. (I) The legal status of the REC is unclear. The regulations of REC construction in China are scattered among the policy documents related to clinical trials, which only define the functional scope of a REC from a macroscopic point of view and lack the relevant rules for guidance and operability. (II) The formation and operating system of a REC lack regulatory provisions. At present, China has not yet set up REC approval, registration, operation, supervision and management and other related regulatory documents. Therefore, RECs are mainly focused on conducting training and providing consultation and less on conducting commissioned reviews. (III) The responsibilities and risks of a REC are unclear. According to the Opinion of the two state offices of China, RECs can undertake the commissioning of a review. Does the commissioning of a review include both initial review and follow-up review? Regarding the review of information related to the institution, such as the review of the investigator's qualifications, is it judged only by looking at the investigator's curriculum vitae? What if the approved investigator has integrity issues or is not medically competent: how is the responsibility of the REC and the institution defined? The responsibilities of RECs are not clearly defined by state statute, so RECs are subject to some limitations when undertaking delegated reviews. (IV) Institutional ethics committees rarely accept the conclusions of REC reviews. Some scholars have reported that only 19.6% of institutional IRBs accept a REC's review comments (7). The Sichuan TCM REC, which has undertaken the largest number of commissioned review projects, also indicated that RECs are mostly accepted by institutions without ethics committees, such as universities and research institutes, and for institutions with IRBs, whether the review conclusions of the ethics committee can be accepted still depends on the institution itself (6). The reason an institutional ethics committee does not accept a REC's review results, in addition to the reasons mentioned above, also involves whether this committee has corresponding SOPs and work procedures to accept these results. At present, most institutions have not yet established this part of their work (8). Therefore, this is also the main reason the REC commissioning review has not been fully carried out.

In addition, the construction of RECs in China is still

in the preliminary exploration stage, and no standards have been formed for the composition of the team, personnel selection and recruitment, review procedures, quality management, and fees, etc. REC reviewers are from different institutions, and most are part-time reviewers. The lack of full-time review experts will have a certain impact on the efficiency of REC reviews. In addition, the geographic region of the RECs can make it very difficult for nonlocal institutions to participate in collaborative ethical reviews of RECs; therefore, the development of professional ethics committees should be actively explored on the basis of RECs, such as pediatric RECs and oncology RECs. Considering the special characteristics of various systemic diseases and populations, a set of ethical review methods for clinical research based on professional fields has been established, and authoritative experts in the industry are responsible for the ethical review of research protocols, investigator manuals and subject-related safety data used to discuss the ethical issues and operability of clinical trials, which can better ensure high-quality ethical reviews and the safety of subjects. At the same time, professional RECs can also discuss in depth how to improve the methods and efficiency of ethical reviews of clinical trials in disease fields, taking into account the difficulties of the discipline, the factors of the subject population and the complexity of ethical reviews, and develop relevant operational guidelines to provide guidance for the work of ethics committees within the institution.

In January 2018, the China Cardiovascular Research Collaborative Group Ethics Committee was established as the first professional REC in China. This Committee aims to improve the efficiency and quality of ethical reviews in the cardiovascular field, and as an independent ethics committee, it receives ethical reviews of multicenter clinical trial projects in this specialized field.

In general, RECs are still in the early stages of development in China. In addition to developing a simplified and smooth review process and reasonable fees, as areas of future exploration, RECs should target strengthening their own personnel to ensure that their tasks are carried out effectively and on time, and exploring other RECs in specialized areas so that ethics collaborative reviews are not limited to geographic areas.

Collaborative ethics review consortium

Collaborative ethics reviews issued by collaborative ethics review consortia and corresponding societies have achieved consensus and are supplementary to the collaborative review conducted by RECs; these entities also refine working procedures on how to conduct collaborative ethical reviews. All of these reviews are based on the rationale of a single IRB (9-12), where each project designates a reviewing IRB, and other participating sites can endorse the ethics opinion of the reviewing IRB and review only the conditions for conducting trials in their own sites. All of these consensuses clarify the basic conditions of the reviewing IRB, which provides some guarantee for the ethical review ability of this IRB and the quality of the project review. The above clarification of collaborative review work procedures and the division of responsibilities have played a positive role in the implementation of collaborative ethical reviews. Among these consensuses, some have been issued by industry-related organizations, allowing all domestic institutions willing to undergo a single ethical review to participate, thus transcending the geographic limitation of RECs, helping improve the efficiency of ethical reviews and promoting the development of clinical trials for multicenter clinical trials conducted across several geographic areas (9). However, these consensuses have not been well implemented since their release, and only a fraction of institutions across the country have participated, thus limiting the implementation of collaborative ethics reviews.

The only exception is the Beijing Consortium for Mutual Recognition of Medical Ethics Review (herein the Consortium). At the end of 2019, the Beijing Municipal Health Commission established the Consortium, and 45 medical institutions enthusiastically applied to join. From among them, the Beijing Municipal Health Commission selected 15 national clinical medical research centers as the first group of Consortium members. Because the value of a collaborative review can only be highlighted by more institutions participating in a multicenter clinical trial, the Consortium further expanded its scope to 48 institutions in March 2021, including 43 tertiary hospitals, 4 secondary hospitals and 1 CDC (Beijing Centers for Disease Control and Prevention). From the establishment of the Consortium on December 1, 2020, to April 25, 2021, nearly 5 months later, 36 of its 48 units achieved mutual recognition of ethical review results as required by the rules. For all Consortium members, one of the fundamental reasons that it can effectively carry out mutual recognition work is that its working rules are issued by the Beijing Municipal Health Commission. Only when the working rules are clearly defined by the administrative authority and the responsibilities and powers of collaborative ethics reviews

are clear can the collaborative review work be carried out smoothly.

Discussion

At present, China has undergone several stages of development ranging from institutional ethics committee reviews (all participating sites conduct ethics reviews) to central ethics reviews (only the central IRB review) and single ethics review/ethics review mutual recognition (the reviewing IRB and the relying IRB engage in mutual recognition), and the ethics review system has gradually been clarified. The main existing problem is lack of mutual recognition of ethics reviews which caused in one same multicenter clinical trial study, each IRB usually performing ethic review by themselves no matter other IRBs completing their review or not, and what's the review conclusion and comments from other IRBs. The efficiency of multicenter clinical trial execution is influenced due to long site start-up period. Therefore, from the top-level design, its strongly recommended to promote the mutual recognition among IRBs in different Chinese hospitals, especially for those in the same Chinese province or area.

The mutual recognition of ethics reviews is an inevitable trend in the development of multicenter clinical research. With the combination of positive policy leadership, strong demand from the research and development market and the intrinsic drive of the ethics review industry itself, the Beijing Health Commission and local medical institutions have taken the first substantive steps to establishing a mutual recognition consortium, formulating working rules, unifying review templates, and launching information platforms. However, for ethics mutual recognition consortia and RECs in other regions, it is still necessary for government departments to issue corresponding policies and further clarify responsibilities and rights. The mutual recognition of ethics is the future direction of collaborative ethical review development, and national and local governments should focus on promoting mutual recognition within each region, within each professional field, and among various types of institutions at all levels. We should establish a unified information platform for ethics reviews, promote the adoption of a unified list by each institution, and promote mutual recognition to effectively improve the efficiency of ethics reviews and medical translations. A concept of "whole-process-linkage" is proposed in the ethic management process of multicenter clinical trials, to establish a cooperative review led by domestic professional institutes, on the basis of extensive and in-depth training exchanges and effective communication on the same platform, collaborative review, ensure quality and efficiency, so as to promote and implement the "mutual recognition" of the ethic review (13). Under the mutual recognition platform, the REC or collaborative ethics review consortium can be relevantly easier to be established and promoted nationally. Some new model like the hybrid ethic review modes can also be explored between some developed regions where their located hospitals having mature experience on central ethic review already. Multiple ethic review mode can be applied as the development status of ethic review system from Chinese hospitals is unbalanced at present. The pilot needs to be encouraged to implemented new modes, thus the good experience and lessons learnt can always be shared between hospital institutions and local governances. The ultimate goal is to improve the overall efficiency of ethic review across regions in China gradually. Besides the pattern of ethical review of multicenter clinical trials, to further improve the efficiency of ethical reviews, some research has discussed the challenges in the ethical review of a particular field's clinical research, such as TCM and coronavirus disease 2019 (COVID-19) treatment drugs. It is proposed that ethics committees should broaden their staff composition with more people with a TCM background or conduct TCM-related training. More internal communications are also necessary to supplement cross-cultural experiences (14). In addition to applying for a standardized ethical review and adhering to the *Key Guidelines on the Ethical Acceptability of COVID-19 Human Challenge Tests* issued by the WHO, clinical trials related to COVID-19 may be controversial or involve higher risks and levels of uncertainty. The COVID-19 relevant scientific knowledge should be necessary for at least one member of an independent ethics review committee. The IRB review process should involve a high level of the necessary knowledge, which is fundamental to make sure the high efficiency of ethic review (15). All IRB members must complete necessary trainings to learn about the policies and procedures of the ethic review as well as the relevant regulations and ethical codes surrounding the conduct of clinical trial research. Currently majority of such available training is designed and conducted by the hospitals themselves and more relevant to GCP itself. It's recommended to establish a national training platform and certificate can be issued to demonstrate the qualification of IRB members. Some industry association can also establish a system to provide the training and educational resources,

which can provide various educational opportunities to assist with building knowledge and competence of IRB members.

The multicenter ethical review should adopt the conditional 'approval' mode of the leading site's ethical review decisions, gradually establish a single IRB review and select the best ethics committee. RECs can gradually take responsibility for the primary review in the multicenter ethics review model and ultimately contribute to improving the mechanism and efficiency of the ethics review. It is believed that with the joint attention and efforts of the government and medical institutions, the ethical review of multicenter clinical trials will achieve real, mutual recognition, effectively improve the efficiency of ethical reviews on the basis of quality assurance and provide good service and support for collaborative innovation in medicine and health in China.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5213/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Detailed search strategy of CNKI database as an example

Items	Specification
Inclusion and exclusion criteria	Inclusion:
	Study type: review or original research article
	Language: Chinese
	Exclusion:
	Study type: dissertation, meeting, newspaper, book, patent, annual, industry standards
	Language: English
Selection process	Step 1: key words: clinical trials
	Step 2:
	Main topic: clinical trials, clinical research, clinical trial research, ethic review
	Secondary topic: clinical trials, clinical research, GCP, IRB, clinical trial institution
	Research level: technical research, clinical research
	Journal: all
	Source: core journal
	After searching in database, 12,513 articles searched. Tiered by relevance and author Jing Ding and Keke Fang reviewed the abstract of the first 200 articles, then downloaded the articles more relevant to this research topic. The final selection of literature and the collection, assembly and analysis and interpretation of data were conducted author Jing Ding, Yashu Yin and Keke Fang. The manuscript was drafted by author Jing Ding, Yashu Yin and Keke Fang, then all authors reviewed the literatures and draft manuscript together, revise subsequentially until obtaining a consensus on the comments

GCP, Good Clinical Practice; IRB, institutional review board.

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