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Perceptions of clinicians and research ethics boards regarding ethical issues in investigator-initiated trials: a multicenter qualitative study in China

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Abstract

Purpose This multicenter qualitative study aimed to explore the perceptions of clinicians and research ethics boards (REBs) regarding ethical issues in Investigator Initiated Trials (IITs).

Methods Between February and April 2024, semi-structured interviews were conducted with 27 participants from 15 tertiary hospitals, including clinical doctors and members of REBs. Responses were grouped and analyzed using a descriptive phenomenological approach.

Results Clinicians expressed challenges in navigating the formal review process due to limited access to information and unclear guidelines. Academic review highlighted a deficiency in research literacy among clinical investigators, leading to flawed study design. Ethical review revealed concerns about inadequate ethical awareness among clinicians, resulting in failed ethical approvals. Moreover, delays in review processes and resource shortages were noted, hindering the efficient conduct of IITs.

Conclusion The findings underscore the need for comprehensive training programs to enhance clinicians' research literacy and ethical awareness. Establishing a comprehensive system to support IITs, including enhanced guidance and support from REBs, is essential to ensure the quality and integrity of IITs in China.

Keywords Ethical issues, Investigator-initiated trials, Clinical researchers, Research Ethics boards

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1 Background

Investigator-initiated trials (IITs) are clinical research conducted by medical and healthcare institutions, investigating human subjects and not necessarily primarily focused on drug or medical device registration. As of April 2024, the Chinese Clinical Trial Registry (www.chictr.org.cn) has recorded a total of 81,770 registered clinical studies, a significant surge from 14,477 in February 2018 in these studies, the majority are clinical trials initiated by clinicians from medical institutions [1, 2]. While IITs seems to be thriving in terms of quantity, concerns persist regarding their varying quality [3, 4]. Additionally, there exist notable international and regional discrepancies in the organization of ethical reviews [5].

Medical research must adhere to ethical standards, with beneficence, nonmaleficence, autonomy, and justice being the four basic principles of ethics review [6]. IITs represents a novel domain for clinical medical practitioners and regulators in China. Currently, there lacks a standardized operational framework, and the practical application of Good Clinical Practice (GCP) to IITs is often challenging [2, 7]. To emphasis quality control of IITs, "Measures for the Ethical Review of Biomedical Research Involving Humans " was issued to further standardize ethical review in 2023 [8]. Moral frameworks or administrative regulations were not enough to solve a dilemma in IITs since guidelines only describe what to aim for and not how to interpret or use them [9].

In addition to ethical related issues, unscientific research is also considered unethical by definition [10, 11].The ethical review process for IITs in China mainly consists of three parts: formal review, academic review, and ethical review [4]. Reviewing research protocols by experts not involved in the study is one way to ensure the protection of human research subjects. Submitting projects for ethical review can be a challenging process, especially when facing subsequent comments or criticisms, which can be occasionally irksome or even distressing [10]. Brian et al. explored the varied definitions of ethical issues among clinical researchers and IRBs, uncovering notable disparities that may have implications for the evaluation of clinical trials [12]. Although previous literature reviews or qualitative studies have addressed ethical issues in research, they have not specifically described those related to IITs [13, 14]. Kimberly highlighted cultural differences in values and understandings created an ethical dilemma [9]. Moreover, there is less empirical research on IIT-related issues in China.

This study seeks to uncover the obstacles and requirements encountered by clinical researchers during the ethics review of IITs, while also examining the perspectives of ethics boards as reviewers. Its findings may help bridge the awareness gap between clinicians and ethics boards in the review process, providing countermeasure reference for promoting the implementation of IITs.

2 Methods

2.1 Study design and participants

A qualitative research approach involving individual semi-structured interviews was used to systematically document ethical issues. The research adheres to the Standards for Reporting Qualitative Research (SRQR) checklist, ensuring transparency and providing an audit trail of the qualitative study process.

Purposive sampling was used to select clinical doctors and ethics boards members from tertiary hospitals across China, ensuring representation from various geographical and economic regions. This selection was conducted between February and April 2024. Inclusion criteria were as follows: (1) Clinicians from public tertiary hospitals who had participated in IITs and had experience applying for ethical review, or personnel involved in ethics boards work at public tertiary hospitals with experience in ethical review of IITs. (2) Willingness to participate in the study and sign informed consent. Exclusion criteria: Clinicians involved in IITs not related to human subjects.

2.2 Data collection

All interviews were conducted by the first author (JL), a registered clinical physician trained in qualitative research. Interviewers introduced the purpose and interview process of the study to the interviewees. Upon obtaining informed consent from the interviewees, the conversations of each interviewee were fully recorded. Semi-structured interview format was employed with interview guidelines developed separately for clinical physicians and ethics board members (Appendix 1–2) [15]. If the participants have multiple, overlapping responsibilities, we would confirm with them which role they wish to participate in.

The interviews were conducted either via online video conferencing or face-to-face meetings. Basic information of the interviewees, such as gender, age, profession, highest education level, relevant work experience, and professional title, was recorded at the beginning of each interview. The interview process followed the interview guidelines, with adjustments made to the questioning method based on the specific roles. Any unclear points were clarified through follow-up questions, restatements, or clarification, and interviewees were encouraged to express their genuine feelings.

2.3 Data analysis

The interviews were recorded using a voice recorder and transcribed verbatim into text files using the WPS audio-to-text within 48 h after the interview.

The accuracy of the transcripts was verified by a researcher (JL), who cross-checked the transcripts with the contents of the audio recordings. Data analysis commenced immediately after obtaining the interview transcripts of the first participant, followed by an ongoing process of comparison and iteration alongside data collection. Two researchers (JL and HY) conducted independent coding and extraction using thematic analysis involving six steps (Appendix 3). NVivo 12 (qualitative data analysis software, QSR International, 2020) was employed to assist with data analysis. A descriptive phenomenological approach was utilized, recommended for documenting the perceptions of ethical issues to identify common codes, subthemes, and themes [16]. Finally, the sample size was determined based on the principle of data saturation, with interviews continued until no new themes emerged.

3 Results

3.1 Baseline demographics

We interviewed a total of 27 participants, including 13 clinical doctors and 14 ethics board members. Among the ethics board members, there were 3 full-time secretaries, 2 part-time secretaries, 6 part-time members, and 3 office directors. The average interview duration was 44 min (ranging from 22 to 67 min), with an average age of 36.8 years (ranging from 25 to 54 years). The interview participants were drawn from hospitals spanning China, comprising 7 (46.7%) from the western regions, 2 (13.3%) from the eastern regions, 3 (20.0%) from the southern regions, 1 (6.7%) from the northern regions, and 2 (13.3%) from the central regions. Table 1 shows the participants' baseline characteristics.

We synthesized 40 codes into 5 subthemes, progressing from descriptive narratives to causal analysis and finally to coping strategies. Subsequently, we distilled these into 3 main themes, visually represented in a Sankey diagram (Fig. 1), illustrating the progression from codes to themes.

3.2 Formal review——insufficient information channels

During the formal review, over half of the clinicians raised concerns about the lack of an effective public channel to access information related to ethical review. Interviewees

Table 1 Demographic characteristics of the study participants

Characteristic	Interviewees, *n* = 27	Clinicians, *n* = 13	Research Ethics Boards, *n* = 14
Mean (SD) age, y	36.8(7.3)	35.6(6.5)	37.9(8.0)
Sex, no. (%)			
Male	12(44.4%)	8(61.5%)	4(28.6%)
Female	15(55.6%)	5(38.5%)	10(71.4%)
Education level, no. (%)			
Undergraduate	5(18.5%)	1(7.7%)	4(28.6%)
Master	10(37.0%)	4(30.8%)	6(42.8%)
Doctor	12(44.5%)	8(61.5%)	4(28.6%)
Geographical distribution of hospitals, no.	15	11	6
Eastern region	2(13.3%)	2(18.2%)	-
South region	3(20.0%)	2(18.2%)	1(16.7%)
North region	1(6.7%)	1(9.2%)	-
Western region	7(46.7%)	4(36.4%)	5(83.3%)
Central region	2(13.3%)	2(18.2%)	-
Medical field of expertise, no. (%)			
Internal medicine	10(37.0%)	3(23.0%)	7(50.0%)
Surgery	5(18.5%)	5(38.5%)	-
Gynecologic	5(18.5%)	5(38.5%)	-
Nursing	1(3.7%)	-	1(7.1%)
Medical laboratory	1(3.7%)	-	1(7.1%)
Health Service Management	1(3.7%)	-	1(7.1%)
Pharmacy	3(11.2%)	-	3(21.4%)
Epidemiology and Health Statistics	1(3.7%)	-	1(7.1%)
Mean years of review/clinical experience, y	-	11.0	4.6

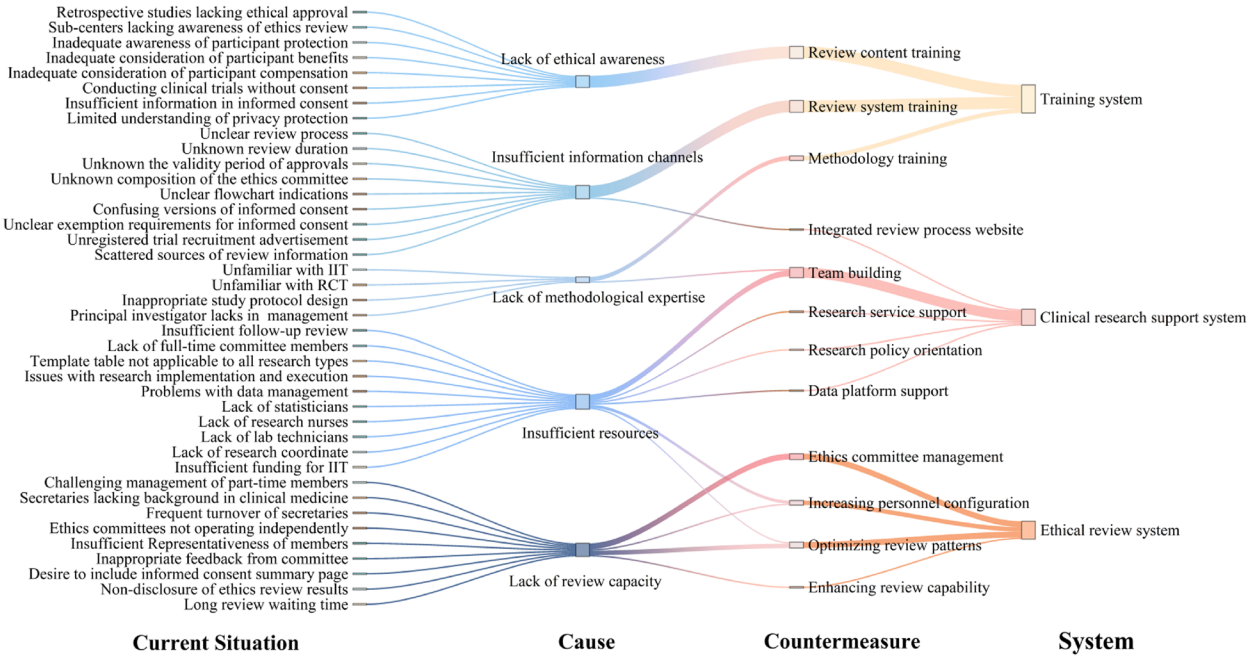

Fig. 1 Sankey diagram of sample codes and their subordination to each theme

were from 15 tertiary public hospitals across China, with only 5 hospitals (1/3) having dedicated websites for review, while others relied on the Office Automation (OA), resulting in limited and fragmented information about the ethical review process and regulations. In some cases, clinicians had to refer to instruction posters posted at the office door, which often lacked crucial information such as key timelines, responsible departments and personnel, making the instructions less informative. As a result, most clinicians remained confused during the ethical review process. For example, 4 clinicians mentioned their uncertainty about the requirements for waiving informed consent, 3 were unclear about the one-year validity period of ethical approvals, and 3 were unsure of the significance of the version labeling on informed consent forms.

Regarding the feedback from the ethics boards, most of the issues align with their actual difficulties during the formal review, but there were still some discrepancies (Table 2). Three clinical doctors noted that the required document templates for submission were not suitable for their research. However, the boards believed that the templates they provided could meet the requirements of the majority of research types. Additionally, clinicians felt that too many document materials were submitted during the review phase, primarily due to a lack of recognition of the distinction between research protocol and project proposal.

"I think the uploaded documents were too complex, with over a dozen files, some of which are unstructured text. I find it challenging to fill them out. I hope the submission requirements can be simplified." (Clinician 11, male, 35-year-old).

"The most common issue is incomplete preparation of documents. Secondly, there's confusion between the research protocol and the project proposal. The proposal is just the preliminary design of the study used for application, focusing on scientific aspects. So, why do we need the research protocol for ethical review? The research protocol is the operational plan for your entire study, involving many details. It's this protocol that reflects the elements we need to review in ethical review." (REB 7, female, 32-year-old).

3.3 Academic review——lack of methodological expertise

During academic review, 10 (71.4%) committee members provided feedback, indicating an overall lack of research literacy. Many clinical doctors intending to conduct IITs lack the experience and training necessary for such research, which can pose challenges during project execution and management. Even for those with some experience, their understanding of the entire research process may be limited, complicating ethical review and project proposal. This deficiency was manifested in unreasonable inclusion criteria, a lack of rationale for sample size

Table 2 Comparison of issues in review process between clinicians and research ethics boards

Review process	Category	Clinicians	Research ethics boards
Formal review	Consistency	Lack of clarity on documentation requirements	Incomplete or missing documents
		Confusion regarding submission process	Unfamiliarity with the review process
		Uncertainty about the significance of different versions of informed consent forms	Not distinguishing or specifying versions of informed consent forms
		Uncertainty about the validity period of ethical approval	Expiration of ethical approval
	Discrepancy	Templates cannot cover all study types	Most types of research can be covered by templates
		Too many forms to fill out	Uncertainty about the distinction between protocols and project declarations
Academic review	Consistency	Difficulties in study design	Unreasonable inclusion criteria and sample size
		Difficulties in study design	Non-standard treatment protocol comparison
		Difficulties in study design	Inappropriate Outcome Measure Selection
		Lack of statistical knowledge	Inappropriate data analysis methods
	Discrepancy	Lack of differentiation between clinical treatment and research intervention	Inadequate risk management plan
Ethics review	Consistency	Limited understanding of ethical principles and standards	Participant protection
		Lack of clarity on participant compensation and rewarding	Participant compensation
		Uncertainty on how to effectively supervise and manage data	Privacy protection
		Lack of details on informed consent procedures	Participant benefit/ Participant self-payment items
		Unclear requirements for waiver of informed consent	Eligibility for waiver of informed consent
	Discrepancy	Lack of summary page in informed consent	Difficult to fully inform patients
		Hope to publicize the results of ethical review	Publicizing involves the privacy of the researchers' subjects

calculation, inappropriate data analysis methods, and inappropriate outcome measure selection (Table 2).

During academic review, there were discrepancies between the REB 's feedback and clinical doctors' perceptions. Clinical doctors' risk assessment plans often addressed clinical treatment risks rather than risks associated with experimental interventions (Table 2), highlighting a fundamental failure to differentiate between treatment and experimental risks [17].

> *"Many doctors have scattered knowledge about IITs; they may have conducted some parts of research or GCP and think they can conduct an IITs. However, they may not understand the entire process of research execution, leading to difficulties in ethical review or project proposal, which may seem challenging and inconvenient at every step. I think this could be a significant issue." (REB 3, female, 44-year-old).*

> *"Some doctors cannot distinguish between clinical treatment and research interventions. For example, in an observational study observing postoperative patients, the surgery itself is not the research intervention. However, researchers may mistakenly perceive the surgery as their research intervention, including the entire surgical process in the protocol, and informing participants of all surgical risks during the informed consent process. In reality, it is an observational study with minimal risks." (REB 7, female, 32-year-old).*

3.4 Ethnic review——lack of ethical awareness

After formal and academic reviews, both clinical doctors and IRB members expressed concerns in the ethical review, 48.1% (13/27) interviewees mentioned insufficient ethical awareness among clinical doctors, particularly in areas such as participant protection, benefits, compensation, and privacy protection. Specifically, issues were noted regarding retrospective studies lacking ethical approval, sub-centers lacking awareness of ethics review, and conducting clinical trials without consent.

> *"In my first retrospective study, I didn't undergo ethics review because I wasn't aware of it during my master's studies. It wasn't until the journal's feedback that I realized even retrospective studies require ethical review. Since then, I've been very mindful of this in subsequent research." (Clinician 7, male, 32-year-old).*

"Overall, there's a general lack of awareness regarding ethics review. For instance, as the primary research unit initiating a project, many sub-centers seem unaware of the necessity of ethics review. Even if the primary center has passed, the sub-centers still need to undergo ethics review or ethics filing." (Clinician 2, male, 31-year-old).

"Some studies lack injury compensation clauses. For IITs, some researchers consider their interventions as routine treatments without harm to participants. However, using data alone carries risks of privacy breaches and potential harm to their rights." (REB 13, female, 32-year-old).
"For example, researchers want to collect small tissue samples, about a few millimeters, from both patients and healthy individuals. They consider this experiment poses no more than minimal risk, but I think it is definitely greater than minimal risk. (REB 6, female, 35-year-old)

In terms of ethical review, feedback from the REB and the perceptions of clinical doctors mostly corroborates each other, indicating insufficient ethical awareness leading to failed ethical review. However, there are certain differences concerning informed consent. Clinical doctors think that informed consent should be adjusted according to the type of study, suggesting that informed consent for observational studies could be more user-friendly and streamlined for better implementation, such as the inclusion of a summary page. The REB also acknowledges this issue, recognizing that lengthy informed consent forms may not effectively inform non-medical participants, necessitating enhanced monitoring to ensure researchers fulfill their obligations in informed consent. Additionally, some doctors advocate for the public disclosure of ethical review results, including details about the project leader and project content, to facilitate peer communication. However, the REB is cautious about disclosing such information due to the privacy of the applicants, particularly in affiliated military hospitals (Table 2).

3.5 Lack of review capacity

During the ethics review, 46.2% (6/13) of clinicians and 14.3% (2/14) of committee members noted a significant delay in the review process, which is typically conducted monthly. Clinicians advocate for a bi-weekly review frequency. The REB attributes part of the prolonged duration to inadequate manpower. Primarily comprised of part-time members, predominantly clinical doctors or university professors, the committee faces challenges in ensuring efficient review and management processes. Consequently, they recommend reducing the number of part-time members and increasing the presence of full-time ones.

Additionally, there are professional issues in the research design, contributing to a cognitive gap between clinicians and the REB. Clinicians pointed out that the suggestions made by the REB are not always accurate; sometimes it is sufficient to simply explain the circumstances of the study rather than fully adopt the suggestions. They hope to increase methodological experts, patient representatives, expertise in bioethics and law, and professionals with various medical backgrounds in committee. Age representation is also important, and young experts should be included. Additionally, it is preferable for the ethics boards to be independent of the management department to ensure fair review.

"In my past experiences, the boards usually consisted of 4–5 members, but among them, I didn't encounter any surgical specialists in my five experiences." (Clinician 8, male, 33-year-old).

3.6 Insufficient resources

During the entire ethics review process, 77% (10/13) clinicians mentioned that there is a shortage of manpower and funding for IITs. They are engaged in clinical work while conducting IITs, which severely limits their capacity. During the project implementation, they hope to have research nurses and research assistants to assist in their studies, and they also need to strengthen cooperation with statisticians and laboratory personnel. In the process of project application and promotion, they hope to receive assistance from research service departments to advance clinical research. However, few domestic hospitals have established such service departments. Currently, existing ethics review institutions mainly focus on review responsibilities, and there is still room for improvement in providing guidance and services for clinical research.

"As young doctors, we lack support from junior colleagues, leaving most responsibilities squarely on our shoulders. Juggling clinical duties alongside research projects proves to be quite challenging. In reality, our energy is spread thin, with data collection and patient follow-ups squeezed into our limited free time, making the workload exhausting." (Clinician 6, male, 36-year-old).

"Another pain point is the lack of supportive roles available to clinical doctors. Whether it's our ethics boards or hospital administration, their roles are administrative rather than supportive. (Committee 3, female, 44-year-old)

4 Discussion

4.1 Training system

This study synthesizes perspectives from both clinical investigators and REBs regarding review process in IITs. While there is generally agreement between the two groups, clinicians' lack of understanding regarding ethical review content, procedures and clinical research methodology reaffirm issues raised by ethics boards. The first identified theme deals with the tendency for researchers to express ignorance regarding ethnic guidelines and review process, which is congruent with findings by Tsoka-Gwegweni within low and middle-income countries [18].

However, when it comes to drafting protocols, cognitive differences arise, such as uncertainty regarding the distinction between protocols and project declarations. The root cause lies in the unfamiliarity with the implementation of IITs and the lack of basic literacy in clinical research [19], one of which is the absence of systematic education on clinical research methodology [20]. Peking University only established the graduate program in clinical research methodology affiliated with clinical medicine in 2013. There are few medical schools in China that offer systematic programs related to clinical research methodology [21]. Similarly, the United States continuously updates medical education to promote clinical research. Brandi et al. proposed a new graduate research nurse program to develop a skilled clinical research nurse workforce [22].

Faced with inadequate pre-medical education, we have both a professional and ethical obligation to continue training and supporting clinical doctors [23]. Significant investment in clinical research training is evident across European Clinical Research Infrastructure Network (ECRIN) countries [24].Physician-scientists, serving as bridges between the laboratory and the clinic, are scarce resources. To equip them effectively, a competency-based training framework, as proposed by Lourdes et al., outlines nine core competencies essential for translating clinical research into medical advancements. They believe a robust national conversation should begin regarding the core competencies of physician-scientists, focusing on balancing training efficiency with skill development throughout the entire continuum of physician-scientist education, from trainees to faculty [25].In theory, the highest level of competency is not required for all members of the clinical research team; instead, specific roles necessitate distinct knowledge, skills, and attitudes. Besides, available online training is an invaluable resource for practitioners who want to obtain additional skills in clinical research.

4.2 Ethnical review system

We reported extended review waiting times, challenges in managing part-time members, and frequent turnover of secretaries, attributed to inadequate manpower. Given the early stage of regulation for IITs in China, characterized by inconsistent oversight across institutions and inadequate manpower, it is imperative to optimize review pattens, enhance review capacity, and strengthen ethical review management. Similarly, the developed countries faces manpower shortages, impacting the effectiveness of Research Ethics Boards in monitoring studies [26]. Sarah et al. underscore the ethical challenges, especially in some emerging fields like AI, urging research ethics boards to enhance their understanding and adapt normative guidelines to emerging ethical dilemmas [13, 27]. Efforts should be made to ensure diversity in potential IRB members [28].

In our study, clinicians expressed a need for support from research service departments, yet such assistance is often lacking in most hospitals. Current ethics review institutions primarily focus on regulations but have the potential to offer better guidance in clinical research, with some experts suggesting transitioning to an advisory and validation system [28].

One of the major challenges with IIT research is that ethical reviews are based on standards designed for Industry-Sponsored Trials (ISTs). These standards are then applied to IIT research, requiring the provision of free clinical trial drugs and participant compensation. While ISTs aim for drug registration, with sponsors heavily investing in the research process and meticulously designing protocols, IITs are initiated by researchers who often have limited preliminary research, funding, and team support. This discrepancy can create significant difficulties for IITs in meeting the same rigorous requirements [29]. Therefore, the development of ethics committees tailored to IITs should be strengthened. Additionally, a management model that includes academic review before ethical review during the IIT initiation process should be established to ensure the scientific validity of projects before they are submitted for ethical review [30].

4.3 Clinical research support system

A successful research program cannot be driven by a single doctor alone, team building is important [31]. Shanghai, a pivotal research hub in China, still falls short in the organization of key roles, to meet basic demands. Ambiguity in key role assignments and the common practice of graduate students directly filling significant research positions exacerbate the situation [32, 33]. Although physicians are vital in creating a culture promoting and fostering research, non-physician staff, such as the research

coordinators, clinical research nurses (CRNs), biostatisticians and methodologists are imperative to the overall success and sustainability of the program [24, 34, 35]. Research nursing, distinct from academic nursing, focuses on participant care and clinical trial management, with a history spanning over 40 years in Europe and America [22]. However, in our country, this field is still in its infancy, with many clinical trials being conducted by part-time clinical nurses [36, 37].

Although the number of IITs is increasing year by year, the high cost of conducting such trials and the difficulty of obtaining funds to cover the high cost are obstacles to their realization [38]. In the study by Chen Jieru et al., the initial approval rate for IITs is significantly lower than that for Industry-Sponsored Trials (ISTs). Perceived bias against clinical applications compared to basic science grant proposals may exacerbate this situation [39]. In Denmark, the rise in domestic IITs is credited to increased project support from academic institutions, highlighting the crucial role of institutional policies in IITS development [2, 40]. Clinician 8, a Chinese physician in Denmark for a postdoctoral fellowship, affirmed this idea.

Without data, there is no research. In addition to scientific research policy and funding support, data platform (e.g., Electronic Data Capture) and data management is also important [4, 41]. Besides, hospitals with dedicated ethics review websites exhibited significantly higher levels of satisfaction among clinical researchers regarding the ethics review process in our study. Thus, a comprehensive clinical research support system is essential to facilitate the smooth conduct of IITs.

5 Limitation

In our study, clinicians were primarily from public tertiary hospitals, so their perspectives may not represent all hospitals in China. The main interviewees were doctors involved in IIT research, along with REB members, secretaries, and office directors. However, we lacked input from nurses, pharmacists, legal professionals, and community workers, which may have created information gaps. These were supplemented through a literature review.

6 Conclusion

In conclusion, this study highlights the multifaceted challenges faced by clinicians and REBs in the ethical review of IITs in China. Addressing these challenges requires concerted multi-faceted efforts to improve research literacy, streamline review processes, and allocate sufficient resources. By bridging the awareness gap between clinicians and REBs and implementing robust training and support mechanisms, the ethical conduct of IITs can be upheld, ultimately advancing clinical research and patient care in China.

Authors' contributions
Acquisition, analysis, or interpretation of data: JL, HY, XW, WZ. Drafting of the manuscript: JL, CL. Concept and design: JL, QS, XW. Critical review of the manuscript for important intellectual content: LH, QS, JZ, SL, Sheraz Markar.

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Data availability
The datasets used analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All procedures involving human participants were conducted in accordance with the ethical standards of the institutional. The study adhered to the principles outlined in the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no conflict of interest.

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