Informed consent in cancer drug clinical trials in China: a narrative literature review of the past 20 years

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Informed consent in cancer drug clinical trials in China: a narrative literature review of the past 20 years

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Abstract

**Background:** Although the number of cancer drug clinical trials is increasing rapidly in China, issues concerning informed consent in this research context are currently understudied. By performing a narrative literature review, we aim to describe the current situation and identify the most salient challenges affecting informed consent in cancer drug clinical trials among adult patients in China since 2000.
**Methods:** We searched Web of Science (WOS), PubMed, Scopus, EMBASE, the Cochrane Library databases, China National Knowledge Infrastructure (CNKI), China Biomedical Literature Database on Disc (CBMdisc), Chinese Scientific Journals Fulltext Database (CQVIP) and WANFANG to identify relevant publications since 2000. Data were extracted by three reviewers on 6 items pertaining to study type, theme and challenges.

**Results:** We identified 37 unique manuscripts, from which 19 full texts were obtained and six were included in the review. A review of references cited by the six eligible studies did not result in identifying additional eligible studies. All six studies were published in Chinese journals, and the publication years of the majority (five out of six) of the studies were 2015 or later. The authors of the six studies were all from clinical departments or ethical review committees at five hospitals in China. All of the included publications were descriptive studies. Publications reported challenges related to the following aspects of informed consent: information disclosure, patient understanding, quality of information disclosure, voluntariness, authorization, and procedural steps.

**Conclusion:** Based on our analysis of publications over the past two decades, there are currently frequent challenges related to various aspects of informed consent in cancer drug clinical trials in China. Furthermore, only a limited number of high-quality research studies on informed consent in cancer drug clinical trials in China are available to-date. Efforts toward improvement of informed consent practice, in the form of guidelines or further regulations in China, should draw on both
experience from other countries and high-quality local evidence.

**Key Words:** cancer drugs, clinical trials, research ethics, informed consent, narrative review

**Background**

Implementation of clinical trials is vital for continuing to develop more effective treatments for cancer, one of the leading causes of death on a global level [3]. An estimated 19.29 million new cancer cases occurred worldwide in 2020, including 4.57 million new cases and 3 million cancer-related deaths in China [1]. China ranks first in the world for both incidence of cancer (accounting for 23.7% of new global cases) and cancer deaths (accounting for 30% of all cancer deaths) [1]. Rates of new cancer cases and deaths in China have been increasing since 2000 [2], and by 2017, cancer became the country’s leading cause of death, constituting 26.1% of all deaths in China [4]. In response, the Chinese government has given increasing priority to researching, developing, and delivering effective cancer drugs.

Research on cancer drugs has been continuously supported since 2009 by the Chinese Major New Drug Innovation Program [5]. Between 2009 and 2018, the number of cancer drug clinical trials in China increased at an average annual rate of 33% [5]. In 2015, despite tightening requirements for market authorization of any drugs that have undergone clinical trials, the State Council of China also adopted less restrictive requirements for researchers to obtain approval for clinical trials [6]. The following year saw further accelerated growth in the number of cancer drug clinical trials, with the number of newly launched trials increasing by 113% between 2015 and 2016 [5]. A total of 2,602 clinical trials, mainly for anti-tumor drugs, were registered in 2020 — an overall increase of 9.1% from 2019 [7]. And the annual growth rate of China's cancer clinical trials in 2020 was 52.3% [32]. Despite the increasing number of trials, a significant but understudied barrier to wider
implementation of cancer drug clinical trials in China is the complexity of the informed consent process [8].

Informed consent is a guiding principle in Chinese and international ethics guidelines. Chinese law requires researchers to obtain informed consent for studies, including clinical trials, in order to affirm the autonomy of participants and protect them from harm [9]. Regulated aspects of informed consent include the text of informed consent forms and the process of informed consent [10]. Obtaining informed consent in cancer drug clinical trials involves unique ethical complications. Participants in these trials are often especially vulnerable — the majority being patients with advanced cancer who have no other therapeutic options, fairly low survival rates, and short remaining life spans [11-12]. High costs associated with cancer treatment are known to impose significant economic burdens on participants and their families [12]. Furthermore, patients with cancer in China frequently have limited to no awareness of their diagnosis [13]. Due to family-oriented values drawn from Confucianism and traditional Chinese cultural attitudes treating the topic of death as taboo, it is common practice for families to conceal information from cancer patients in an effort to protect them from despair. Research suggests physicians in various cultures find delivering news about cancer to patients to be a highly stressful experience, and China is no exception [15]. Despite ongoing changes to clinical informed consent laws in China emphasizing the need to inform patients directly of medical information, and despite an increasing proportion of cancer patients who report they would want to be informed, oncology clinicians still tend to defer to families who prefer concealing information from patients [13,16-17]. Information that clinicians and families conceal from patients may include diagnosis, prognosis, and details about treatment options.

In 2003, China issued its first "Good Clinical Practice for Drugs" (GCP) guidelines, clearly emphasizing ethics committees and informed consent as the main measures to protect the rights and interests of study participants [18]. On the basis of GCP, the Chinese "Guidelines for Review Work" describe informed consent as the most
important aspect of drug clinical trials for ethics review committees to evaluate [8]. The revised GCP in 2020 established stricter and more detailed regulations on the content and signature process of informed consent forms [19]. Since 2019, a number of other general laws and laws in the field of drug clinical trials have raised the acquisition of informed consent from research participants to the legal level. The Basic Medical and Health Care and Health Promotion Law, the Common Law, and the Drug Administration Law all stipulate that investigators conducting medical research, including drug clinical trials, must obtain informed consent from participants [20].

In light of changing clinical trials regulations and the unique cultural factors concerning care for cancer patients in China, there is a particular need for research to examine informed consent in cancer drug clinical trials. This narrative review study aims to describe the current situation and identify challenges affecting informed consent in clinical trials of cancer drugs among adult patients in China since 2000.

Methods

Search strategy

Publications from 2000 to 2020 were comprehensively searched. A literature search was conducted in the following digital databases: Web of Science (WOS), PubMed, Scopus, EMBASE, and the Cochrane Library databases, China National Knowledge Infrastructure (CNKI), China Biomedical Literature Database on Disc (CBMdisc), Chinese Scientific Journals Fulltext Database (CQVIP) and WANFANG. We used the following search words: cancer/tumor/oncology/neoplasm, informed consent, clinical trial, ethic/ethics/ethical, China/Chinese. We used the following search terms: (1) (“cancer” or “tumor” or “oncology” or “neoplasm”) AND “informed consent” AND “clinical trial” AND (“China” or “Chinese”); (2) (“cancer” or “tumor” or “oncology” or “neoplasm”) AND “informed consent” AND “clinical trial” AND (“China” or “Chinese”).
or “neoplasm”) AND “informed consent” AND “clinical trial” AND (“ ethic” or “ethics” or “ethical”) AND (“China” or “Chinese”). Search terms were different according to different databases. Specific strategies for each database are presented in Appendix 1. We conducted additional review by hand-searching for other relevant publications cited in the reference section of the included publications.

Selection criteria and screening

We included both original studies and reviews related to the current situation or challenges affecting informed consent in clinical trials of cancer drugs among adult patients in China. Publications were excluded if they were: (1) correspondence, editorials, or conference abstracts; (2) studies not written in Chinese or English; (3) studies not available in full text; (4) studies on informed consent in clinical trials among children or adolescents; (5) clinical trials of drugs that did not specify a target disease; (6) studies exploring how informed consent should be implemented; (7) clinical trials of medical instruments or new technologies rather than drugs, or clinical trials conducted outside China; or (8) studies on ethical issues in targeted clinical trials for cancer drugs that did not mention informed consent.

All publications identified according to these criteria went through title and abstract screening and then full-text screening, with both conducted independently by authors WZ and XL. We resolved disagreements by consensus during group discussions among the three authors (XL, XRL, XMW).

Data extraction and analysis
From each included publication, we extracted: (1) the year of publication; (2) first author information, including names and institutions; (3) study design; (4) clinical trial phase number or other classification; and (5) qualitative or quantitative data on informed consent, including but not limited to informed consent forms, implementation procedures, knowledge, experience, and satisfaction among researchers or participants. As our review was restricted by the limited number of eligible publications, only six publications were included in the final analysis. We summarized and reported all relevant information narratively without performing additional statistical analysis.
61 records identified through four Chinese databases

22 records identified through five international databases

37 records after duplicates

18 records excluded after title-abstract screening

19 publications for full-text

Bibliographies analyzed, no additional relevant

13 publications excluded because:
- normative studies (n=3)
- clinical trials outside China (n=1)
- clinical trials for diseases other than cancer or unspecified (n=4)
- editorials/conference abstracts (n=2)
- ethical issues with insufficient information on informed consent (n=1)
- ethical issues in clinical practice rather than clinical trials (n=1)

6 publications included

Fig. 1. Flow diagram for the selection of studies
Results

Among the 37 publications initially identified (Appendix 2), only six met selection criteria. Review of the references cited by the six eligible studies did not result in identifying additional eligible studies (Figure 1). The publications included for final analysis are listed in Table 1. All six studies were published in Chinese journals, and the publication years of five out of the six studies were 2015 or later. The authors of the six studies were all from clinical departments or ethics review committees at five hospitals in China. All of the included publications were descriptive studies, four of which provided a general overview of current implementation or challenges related to informed consent in cancer drug clinical trials based on the literature or the authors’ own experiences. The other two provided results based on questionnaires completed by cancer patients. Based on the data extracted, included publications reported challenges related to the components of informed consent detailed below.

Table 1. Included publications

<table>
<thead>
<tr>
<th>Title</th>
<th>Author</th>
<th>Institutions</th>
<th>Publication year</th>
<th>Study type</th>
<th>Themes and challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethical Issues of Illiterate Patients in Clinical Trials of Anti-cancer Drugs</td>
<td>Hong, D., et al. [27]</td>
<td>Zhejiang Cancer Hospital</td>
<td>2015</td>
<td>Descriptive; narrative based on literature and author experience</td>
<td>Ethical issues, including informed consent among illiterate patients</td>
</tr>
<tr>
<td>Title</td>
<td>Authors</td>
<td>Department/Institute</td>
<td>Year</td>
<td>Methodology</td>
<td>Ethical Issues</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Analysis and Countermeasures of Common Ethical Issues in the Medical Clinical Trial Implementation in Oncology Department</td>
<td>Li, A.M., et al. [23]</td>
<td>Department of Oncology, the First Affiliated Hospital of Zhengzhou University</td>
<td>2016</td>
<td>Descriptive; narrative based on literature and author experience</td>
<td>Ethical issues, including informed consent implementation</td>
</tr>
<tr>
<td>The Patient’s Informed Consent in Clinical Trial of Anti-tumor Medicine Research</td>
<td>Jiang, K., &amp; Zhang, Y. [21]</td>
<td>Department of Oncology, The Second Affiliated Hospital of Dalian Medical University</td>
<td>2017</td>
<td>Descriptive; narrative based on literature and author experience</td>
<td>Problems existing in the process of informed consent</td>
</tr>
<tr>
<td>Investigation and Thinking of Tumor Patients’ Understanding of Clinical Research Ethics</td>
<td>Wei, Y., et al. [25]</td>
<td>Department of Oncology, Radiotherapy and Chemotherapy, Zhongnan Hospital, Wuhan University</td>
<td>2017</td>
<td>Descriptive; cross-sectional survey; consecutive sampling in one hospital; 81 cancer patients but non-participants of clinical trials</td>
<td>Patients’ knowledge and attitudes toward clinical trials and related ethical issues, including informed consent</td>
</tr>
<tr>
<td>Specialty and Related Medical Ethical Issues in Clinical Trials of Anticancer Drugs</td>
<td>Zhang, L., et al. [24]</td>
<td>Medical Ethics Committee, Peking University Cancer Hospital &amp; Institute</td>
<td>2017</td>
<td>Descriptive; narrative based on literature and author experience</td>
<td>Ethical issues, including informed consent implementation</td>
</tr>
</tbody>
</table>
Information disclosure

In practice, treatment alternatives, side effects, and toxicity of drugs being researched were often only partially disclosed or entirely undisclosed to patients participating in clinical trials [21]. In a survey on quality of informed consent in cancer drug clinical trials, 55.9% of 170 participants reported that “doctors did not offer any alternatives besides treatment in a clinical trial” and 41.2% reported not being sure whether doctors had offered information about alternative treatments [22]. Another common problem that patients cited was that investigators used complicated technical terms without adequate explanation when disclosing information or when providing informed consent forms [21,23-24].

Patient understanding: quality of information disclosure

Due to the aforementioned challenges related to information disclosure, therapeutic optimism and other misconceptions were prevalent. Many participants in clinical
trials believed that the drug or treatment being researched was the only effective or the best one for their cancer [21]. Results of a survey showed that over 70% of participants in cancer drug trials trusted clinical trials as the best treatment; 80% mistakenly believed that drugs in clinical trials would not cause severe side effects; and 91.2% of participants mistook clinical trials as the standard treatment [22]. Without sufficient explanation from professionals, cancer patients also reported difficulty in understanding the meaning of key terms in clinical trials, such as “randomization” and “placebos” [21]. In addition, patients’ knowledge regarding their rights and obligations during a clinical trial was insufficient [23]. For example, less than 60% of patients with cancer were aware of their right to withdraw from a clinical trial [22,25].

**Voluntariness**

Valid informed consent requires voluntariness, which refers to freedom from coercion or persuasion [26]. However, to facilitate subject recruitment, investigators may exaggerate the potential therapeutic effect of clinical trials, understate the potential harms or side effects, or blur the distinctions between treatments and clinical trials [21,27]. Clinicians often emphasize the reduction or waiving of medical fees to recruit patients to participate in clinical trials [21]. Such efforts to attract potential participants can erode the voluntariness of informed consent. In some even more direct cases, coercion or pressure on patients to join clinical trials was also reported. Sources of pressure included family members and/or clinicians [21].
Authorization

Previous research has shown that oncology clinicians in China communicate primarily with family members, and many family members partially or completely conceal information from cancer patients [31]. Relatedly, for certain treatment decisions in cancer drug clinical trials, investigators valued the preferences of family members more than patients — which raises ethical questions about the extent to which patients' informed consent is currently being obtained [21,24]. In some cases, family members’ informed consent was mistakenly considered to be an adequate replacement for patients' informed consent, especially when patients were illiterate [27].

Procedural issues of informed consent

In the practice of informed consent in cancer drug clinical trials, there were common errors related to procedures, including: (1) both clinical investigators and patients sometimes failed to sign consent forms after patients orally agreed to participate [21,23], (2) some signed informed consent forms were missing signature dates [23], and (3) many patients and even clinical researchers did not know that patients should receive duplicate copies of signed informed consent forms [23,25]; therefore, it was commonly found that no copies of documents related to informed consent had been provided to study participants [21].

Discussion

Cancer is a major public health problem in China, and the number of cancer drug clinical trials is increasing rapidly. This paper provides the first attempt to
comprehensively review all relevant studies on informed consent in cancer drug clinical trials in China. Our results show that there is limited research on this topic to-date, despite its public health importance. Chinese researchers have begun to note issues faced uniquely by participants in cancer drug clinical trials, and to conduct research specifically on informed consent in that research context.

We found that all authors of the studies included in this review held positions at hospitals. Clinical staff are the main practitioners of research ethics in China, with their ethical knowledge and awareness increasingly being promoted by the establishment of Institutional Review Boards (IRBs). The expansion and regulation of IRBs in China is, therefore, fundamental to continued improvements to ethical practice in clinical trials. The concept of an IRB was first introduced in China in 1987 [33]. University-affiliated hospitals began to establish IRBs in the 1990s, as biomedical research activities grew rapidly. Since 1995, several regulations issued by the National Health Commission (NHC) and National Medical Products Administration (NMPA) have stated that every clinical pharmacology research institution should establish an IRB. In 2007, IRBs for hospitals and their specific working procedures for research ethics review were legally stipulated by the Measures for the Ethical Review of Biomedical Research Involving Humans (For Trial Implementation) issued by China’s Ministry of Health [33-34]. In developing and updating its IRB regulations, China has made its national standards for research ethics reviews increasingly consistent with international guidelines — taking a significant stride forward in 2017 when it officially joined the ICH-GCP [20]. In line with the
development of IRBs and relevant regulations, research on practical issues of research ethics conducted by clinical staff has begun to emerge and increase gradually [35]. Future research on information disclosure, patient understanding, procedural issues of informed consent and other challenges concerning informed consent is warranted.

Despite the fact that only a few publications were included in our sample, we found a large number of challenges reported across almost all aspects of informed consent. The challenges related to the informed consent procedures should be considered within the context of China’s aforementioned relatively late development of IRBs and related regulations, as well as insufficient knowledge and awareness of ethics among stakeholders in clinical trials. Many other challenges such as those related to information disclosure, and participant understanding and voluntariness, are not unique to China, and exist in countries with a much longer history of established IRBs. For example, in studies in Sweden and the United States, investigators are reported to have concerns about the impact of adequate disclosure on participant recruitment, and they observed that disclosure forms lack important elements of informed consent [14, 36]. Similarly, literature from various countries highlights the over-complexity of technical terms used in trials, along with poor understanding by participants regarding randomization, the use of placebos, risks, and the uncertainty of benefits [26, 37]. The issue of voluntariness arises especially in studies in developing countries, where participants are more likely than their counterparts in developed countries to report pressure from fear of the consequences of refusal or withdrawal [38]. Therefore, it would be simplistic to attribute all challenges observed in our
analysis to China’s shorter history of IRBs, and it would also be unrealistic to expect that they can all be overcome quickly. However, as IRBs and related regulations in China continue to develop and expand, China can learn from and tailor lessons and strategies gleaned from other countries’ experience with ethical review of cancer drug clinical trials.

As for the issue of family members giving authorization for patients to participate, literature in other countries also recognizes that a patient’s decision to participate in a clinical trial often involves his or her family members and/or caregivers. The ethical principle of patient autonomy suggests that researchers should ensure patients make the final decision about whether to participate, when resolving conflicts between the interests of patients and those of their relatives [12]. Because research ethics guidelines in China must fit the context of its family-oriented culture, which differs from more individualistic Western cultures [39], further research is needed to examine the cultural suitability and feasibility of methods to ensure patients make the final decision concerning participation in clinical trials. Efforts toward improvement of informed consent guidelines or regulations should reflect local values and be based on local expertise. Not only descriptive studies but also intervention studies should be conducted to establish high-quality, local, evidence-based practice in the future.

Limitations

Due to the limited number of studies currently published on the topic examined in this review, the publications analyzed constituted relatively little original data, as 4 of the
6 used expert opinions as the main data source. Research based on expert opinions, without additional quantitative data collected via validated instruments, carries the risk of reporting bias, because the information is based on the authors’ own experiences and cannot be generalized to understand how widely and acutely the proposed challenges related to informed consent affect China’s cancer drug clinical trials. This limitation also implies limited potential to compare the results of this review with research in other countries. The two publications included in our review that were based on cross-sectional surveys, rather than expert opinion, had samples that were small in size and recruited from single hospitals, limiting the representativeness of their results.

Our analysis also indicated existing studies on this topic in China discussed issues of informed consent without considering different phases of clinical trials or different types of cancers, which further limits generalizability. It is worth noting that studies outside China have found different characteristics among different subgroups of patients, regarding informed consent in clinical trials. For example, participants in phase-I clinical trials are more likely to have misconceptions related to therapeutic optimism and less likely to understand the purpose of clinical trials than participants in clinical trials of later phases [26].

**Conclusion**

As the number of cancer drug clinical trials grows rapidly in China, the question of how to conduct research ethically is becoming an issue of increasing concern for
Chinese clinicians and researchers. Based on our analysis of relevant publications over the past two decades, there are currently frequent challenges related to various aspects of informed consent in cancer drug clinical trials in China. Furthermore, a limited number of high-quality research studies on informed consent in cancer drug clinical trials in China are available to-date. Efforts toward improving informed consent practice, in the form of guidelines or further regulations in China, should draw on both experience from other countries and high-quality local evidence.

**Declarations**

**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Not applicable

**Availability of data and materials**

Not applicable

**Competing interests**

The authors declare that they have no competing interests

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**Authors' contributions**

XL designed and conceived this research. XMW and XRL conducted the literature review, and wrote the main manuscript text. WZ prepared tables 1-4. XRL conducted statistical analysis. KK, XS and JH critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Not applicable
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Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix1.pdf
- Appendix2.pdf