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NEWS AND VIEWS

Reflections and insights into the evolution of restrictive eligibility criteria for cancer clinical trials in China and beyond

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Trial eligibility criteria, which define an appropriate evaluable population through inclusion and exclusion criteria, are fundamental for reliable evidence and should be tailored to the question that the trial sets out to answer [1]. However, exclusion criteria for cancer trials have become increasingly restrictive over the years, with the median number increased from 21 in 1986 to 46 in 2016 [2, 3]. These restrictive exclusion criteria have created substantial barriers to patient access to novel therapies, hindered trial recruitment and limited the generalizability of trial results, presenting not only practical and scientific problem, but also raises important issues of equity that affect everyone [4].

While this longstanding issue has garnered widespread attention in the United States (US), research on the severity of restrictive criteria and efforts to modernize them in China remain scarce [5]. Our limited study revealed that the restriction rate for older patients aged over 75 years in cancer trials in China was 56.5%, which is more than 10 times higher than that of the US [5]. Meanwhile, significant shifts in patterns of exclusion criteria, such as brain metastases from conditionally excluded to not excluded, have been observed in the US since a joint recommendation on broadening cancer eligibility criteria was made in 2017 [6]. The above observations inspire us to understand the potential drivers behind the evolution of overly restrictive exclusion criteria, and provide insights into best practice towards modernizing eligibility criteria in China and beyond.

Regarding to the evolution of overly restrictive eligibility criteria, several fundamental factors should be emphasized. The fundamental consideration about who should be recruited is the future application of the results. Logically, those eligible for a trial should be those who are deemed beneficial from using the treatment in the future. However, when the approved indications are not impacted, sponsors and researchers tend to exclude weaker patients and recruit healthier ones due to excessive concerns about vulnerable populations and drug risk-benefit profiles. This tendency is evident in the fact that most cancer trials in the US enroll healthier patients, such as those with no brain metastases (77.4%), better performance status (PS) (65%) [7].

List of abbreviations: CAR-T, Chimeric antigen receptor T cell; FDA, Food and Drug Administration; PS, Performance status; R&D, Research and development; RWD, Real-world data; US, United States.

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Exclusion criteria are often applied in series, meaning that participants meeting any one of the criteria are eliminated. However, many common criteria, when used alone may not represent manifestations of the underlying malignancy or the potential risk-benefit profiles. For instance, if a therapy does not undergo hepatic metabolism and is not expected to cause hepatic toxicity, strict hepatic function eligibility criteria may not be necessary, or there should be very broad entry criteria. Therefore, it is essential to consider the principle behind each exclusion criterion: should it limit all groups suspected to be at risk, or only those for whom there is a clear basis for harm? The US Food and Drug Administration (FDA) has recommended that items like laboratory values should be used as exclusionary criteria only when clearly necessary to mitigate potential safety concerns, as stated in its newest guidance for cancer trials [8].

Study investigators and regulators are chronically risk averse. The tendency to enroll healthier patients is reinforced by the prevailing review principles of ethics committees, which focus on protecting the safety of trial participants, especially vulnerable ones. In practice, this often causes sponsors and investigators to be overly conservative in designing eligibility criteria to avoid potential questions from ethics committees and to initiate trials as quickly as possible, despite depriving patients of access to new therapies. Real-world studies on chimeric antigen receptor T cell (CAR-T) therapy included 43% of patients who did not meet the inclusion criteria for clinical trials, such as those with poorer PS, older age, and heavier tumor burden, yet the safety and efficacy outcomes were comparable [9]. Ethics committees must recognize that while eligibility criteria are important for protecting participants from treatment-related risks when applied appropriately, overly restrictive criteria can have unintended consequences. The latest issued guideline for good clinical practice explicitly calls for scientific goal should be carefully considered so as not to unnecessarily exclude participants as part of ethical principles [10].

The tendency of restrictive exclusion criteria has gone even far as some eligibility criteria may have commonly accepted over time or used as a template even when they may not apply. Some exclusion criteria are accepted over time through using as a protocol template, regardless of the mechanism of investigational drugs and knowledge of intended indications [11]. For instance, the exclusion of patients with organ dysfunction in cancer trials on chemotherapy drugs is a typical case of unselective reservation of exclusion criteria. Immune-related cancer trials, such as those evaluating immune checkpoint inhibitors, immunomodulators that activate patient's immune response to destroy tumors often use multiple eligibility criteria related to hematologic parameters, even though these trials are not associated with severe hematologic toxicity [2]. Consequently, the number and complexity of eligibility criteria in cancer trials have risen remarkably over the past decades [2, 3]. This leads to a critical issue where a certain proportion of patients are excluded from participating in trials without strong medical or scientific justification considering the mechanism of action of the drug, targeted patient population and anticipated safety.

In addition to a shared understanding of the causes of restrictive inclusion criteria, we propose the following best practices to modernize eligibility criteria. First, all stakeholders related to cancer drug research and development (R&D) needs to develop a basic consensus that unless there is a strong medical or scientific justification otherwise, all appropriate patients should have the opportunity to be included in trials to ensure they equally benefit from new therapies, especially those without standard care. For example, if there is sufficient preclinical or similar drug evidence demonstrating that the drug has specific hepatotoxicity, then strict exclusion criteria should be applied to patients with baseline liver function impairment. They must not lose sight of why this inclusion is important. In designing eligibility criteria, the rationale for exclusionary criteria lacking clear scientific justification should be fully considered, especially when used alone.

Second, to reduce carryover effects from poorly-established or inappropriate eligibility criteria in previous trials, sponsors and investigators should spend additional time and resources ensuring that eligibility criteria are scientifically justifiable in every individual study. Third, to design inclusive trials, sponsors can engage expert clinicians and patient advocacy groups to ensure that the needs and priorities of specific populations are addressed. For instance, involving gerontologists in designing clinical trials that anticipate enrolling primarily older adults can be beneficial. Methodological experts may be helpful for using alternative trial designs to support broader inclusion, such as pragmatic clinical trials or leveraging real-world data (RWD).

Fourth, regulatory guidelines should be formulated, released, and trained on as soon as possible, not only for sponsors and investigators but also for ethics committees, to facilitate the reasonable formulation and review of clinical trial criteria. We summarized related guidelines on cancer trial eligibility by the US to provide a good reference for other countries (Table 1). These guidelines cover clear enrollment recommendations for different populations, suggested strategies to mitigate uncertainties about including them, and encourage trials to be more inclusive by requiring additional analyses and considering the potential impact on product labeling. Discussion with the FDA is generally recommended.

TABLE 1 FDA guidance on cancer-specific clinical trial eligibility criteria.

FDA guidance	Issue date	Main recommendation
Inclusion of Older Adults in Cancer Clinical Trials	2020/03	1. Older adults should be enrolled in all phases trials, including those with frailty; 2. Sponsors should develop inclusive trial design, recruitment strategies targeted to older patients.
Cancer Clinical Trial Eligibility Criteria: Minimum Age Considerations for Inclusion of Pediatric Patients	2020/07	Eligibility of a specific pediatric population should be considered when there is strong scientific rationale for potential benefits and acceptable risks.
Cancer Clinical Trial Eligibility Criteria: Brain Metastases	2020/07	1. Thoughtful consideration should be given to include patients with brain metastases in the context of metastases types, drug mechanisms, available therapies and others; 2. Patients with stable brain metastases should be included unless with strong rationale, while patients with active brain metastases or leptomeningeal metastases should not be automatically excluded.
Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies	2020/07	1. Thoughtful consideration should be given to include patients with organ dysfunction or prior or concurrent malignancies; 2. Detailed recommendations for exclusion of patients with renal, cardiac, hepatic function impairment and prior or concurrent malignancies was given; 3. Patients with prior or concurrent malignancy should generally be eligible.
Cancer Clinical Trial Eligibility Criteria: Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections	2020/07	1. Exclusion of patients with HIV, HBV, or HCV infections should be considered carefully and justified with a disease- and drug-specific scientific rationale in protocols; 2. Recommendations for patients with concurrent HIV infection are based on immune function and HIV therapy; 3. Recommendations for patients with chronic HBV or with history of chronic HCV or virologically suppressed on HCV treatment are based on liver-related laboratories and HBV/HCV therapy.
Cancer Clinical Trial Eligibility Criteria: Laboratory Values	2024/04	1. Laboratory values should be used as exclusionary criteria only when clearly necessary to mitigate potential safety concerns; 2. Laboratory eligibility criteria should be adjusted based on additional available clinical data.
Cancer Clinical Trial Eligibility Criteria: Performance Status	2024/04	1. Patients with lower performance status should be generally included in trials, and the rationale should be described in protocols in case of exclusion; 2. Additional assessments or alternative design was recommended to better characterize the functional status of patients at baseline and over time; 3. Related discussion with FDA was encouraged when appropriate.
Cancer Clinical Trial Eligibility Criteria: Washout Periods and Concomitant Medications	2024/04	1. Exclusion criteria of washout periods and concomitant medications should be justified with a disease- and drug-specific scientific rationale in protocols; 2. Pharmacokinetics and pharmacodynamics should be accumulated and incorporated to inform decision-makings.

Abbreviations: FDA, Food and Drug Administration; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

Notably, we should avoid swinging from one extreme to another. We suggest selectively broadening eligibility criteria, based on regulatory guideline, high-quality evidence or rational medical judgment. Unselectively broadening may result in including trial participants who cannot benefit from the treatment and may jeopardize participant safety. The eligibility criteria for clinical trials represent a double-edged sword; maintaining a balanced approach is crucial and never an easy task. Therefore, accumulating evidence on how to modernize trial eligibility criteria scientifically is also expected in China and beyond. A feasible framework for conducting related research combining of RWD and artificial intelligence strategy has been put forward from US, and a similar study using RWD from China is ongoing [12, 13].

In summary, the subjective willingness of sponsors and investigators, conservative principle of ethic committees, and over reliance on template in protocol design are the three main drivers for overly restrictive exclusion criteria in clinical trials. To modernize these criteria and achieve population diversity in underserved countries like China and others, it is imperative for all stakeholders to form a consensus that all cancer patients should be afforded the opportunity to be included in trials, and to adopt best

practice, especially for sponsors, regulatory agencies and ethics committees.

AUTHOR CONTRIBUTIONS

Huiyao Huang and Ning Li devised the idea for the article, and Jinling Tang also contributed to shaping the idea of the paper. Huiyao Huang and Huilei Miao drafted the first draft and all authors contributed to the writing of subsequent version. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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REFERENCES

1. Rothwell PM. External validity of randomized controlled trials: "to whom do the results of this trial apply?". Lancet. 2005;365(9453):82–93.
2. Garcia S, Bisen A, Yan J, Xie XJ, Ramalingam S, Schiller JH, et al. Thoracic Oncology Clinical Trial Eligibility Criteria and Requirements Continue to Increase in Number and Complexity. J Thorac Oncol. 2017;12(10):1489–95.
3. Peterson JS, Plana D, Bitterman DS, Johnson SB, Aerts H, Kann BH. Growth in eligibility criteria content and failure to accrue among National Cancer Institute (NCI)-affiliated clinical trials. Cancer Med. 2023;12(4):4715–24.
4. Giantonio BJ. Eligibility in Cancer Clinical Research: The Intersection of Discovery, Generalizability, Beneficence, and Justice. Clin Cancer Res. 2021;27(9):2369–71.
5. Huang H, Tang Y, Wu D, Meng X, Wang S, Wang J, et al. Unfair older patients restriction in cancer drug trials in mainland China and corresponding solution. BMC Geriatr. 2023;23(1):199.
6. Xiao H, Vaidya R, Hershman DL, Unger JM. Impact of Broadening Trial Eligibility Criteria on the Inclusion of Patients With Brain Metastases in Cancer Clinical Trials: Time Series Analyses for 2012-2022. J Clin Oncol. 2024;42(16):1953–60.
7. Jin S, Pazdur R, Sridhara R. Re-Evaluating Eligibility Criteria for Oncology Clinical Trials: Analysis of Investigational New Drug Applications in 2015. J Clin Oncol. 2017;35(33):3745–52.
8. U.S. Food and Drug Administration. Cancer Clinical Trial Eligibility Criteria: Laboratory Values. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cancer-clinical-trial-eligibility-criteria-laboratory-values. Accessed on October 1th, 2024.
9. Nastoupil LJ, Jain MD, Feng L, Spiegel JY, Ghobadi A, Lin Y, et al. Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium. J Clin Oncol. 2020;38(27):3119–28.
10. U.S. Food and Drug Administration. ICH HARMONISED GUIDELINE GOOD CLINICAL PRACTICE (GCP) E6(R3). https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf. Accessed on January 22th, 2025.
11. U.S. Food and Drug Administration. Evaluating inclusion and exclusion criteria in clinical trials. https://www.fda.gov/media/134754/download. Accessed on April 4th, 2024.
12. Liu R, Rizzo S, Whipple S, Pal N, Pineda AL, Lu M, et al. Evaluating eligibility criteria of oncology trials using real-world data and AI. Nature. 2021;592(7855):629–33.
13. Huang H, Jia S, Wang X, Miao H, Fang H, He H, et al. Quantitative evaluation of the impact of relaxing eligibility criteria on the risk-benefit profile of drugs for lung cancer based on real-world data. Thorac Cancer. 2024;15(14):1187–94.

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