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# Recent landscape and trends for industry-sponsored pediatric clinical trials in China from 2013 to 2022

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## ABSTRACT

**Importance:** Pediatric medication is a challenging issue globally. Promoting trials of medications for children and implementing measures to encourage innovation for addressing unmet medical and health needs are important.

**Objective:** To explore the recent landscape of pediatric clinical trials of new investigational drugs conducted by pharmaceutical enterprises in China from 2013 to 2022 to provide insight into pediatric drug development in the pharmaceutical industry and regulatory policy formulation.

**Methods:** We performed a cross-sectional observational investigation of pediatric clinical trials registered from January 1, 2013, to December 31, 2022, on the Registration and Information Disclosure Platform for Drug Clinical Trials, the official registration platform established in 2013 for trials of new investigational drugs initiated by biopharmaceutical enterprises. Trials that included pediatric participants (under 18 years old) were retrieved, and their relevant characteristics were extracted and analyzed.

**Results:** In total, 895 pediatric clinical trials were collected, accounting for 5.1% of the total registered clinical trials initiated prior to January 1, 2023. The overall average annual growth rate for the number of pediatric clinical trials was 12% ($P < 0.001$). Phase III trials accounted for the highest proportion (49.1%, 439). Of the 895 trials included, 736 (82.2%) were domestic trials, and 159 (17.8%) were international multicenter trials. In terms of tested drugs, investigations of biological products accounted for the largest proportion of trials (67.4%, 603). Among pediatric clinical trials, studies of vaccines accounted for the largest proportion of trials (41.0%, 367), followed by trials for rare diseases (17.2%, 154). Furthermore, geographical distribution analysis revealed that the largest and smallest numbers of trials were conducted in North China (35.7%, 320) and Northeast China (0.8%, 7), respectively.

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**Interpretation:** The growth trends for industry-sponsored clinical trials involving children illustrate the progress and increasing capability of pediatric drug development achieved in China since 2013. Current challenges and potential areas of focus for policymakers and stakeholders include investigating orphan drugs for rare diseases according to the unique epidemiological characteristics of Chinese children, expanding the scope of pediatric clinical trials, and improving the uneven geographical distribution of leading research centers.

**KEYWORDS**
Geographic distribution, Pediatric clinical trials, Pediatric medication, Rare disease

## INTRODUCTION

The lack of safety and efficacy data for many pediatric medicines is of global concern.[1] In China, pediatric drugs have difficulty meeting the needs of the patients in terms of drug types, dosage forms, and specifications. Promoting safe drug application in children is a long-term health goal. However, pediatric drug development is a challenging process. The relatively small size of this population, the difficulty in enrolling subjects into trials, the uncertainty in reference data extrapolation, and the need to meet strict subject protection regulations limit the evolution of drug development.[2,3] Improving the quality and quantity of pediatric clinical trials can significantly contribute to innovative drug development for children.

However, pediatric clinical trials are more challenging than those for adults due to the paucity of funding, particularly because of cautious ethical considerations given the target group.[1,4,5] A backlog of pending applications caused by a complex approval process and the lack of staff particularly hindered drug availability before 2013.[6] Over the past decade, and especially since 2014, the Chinese government has issued a series of policies and regulations to open the priority review mechanism for pediatric medication and promote the sustainable and healthy development of pediatric health services. The former National Health and Family Planning Commission and other departments jointly issued "Several Opinions on Ensuring Drug Use in Children" ([2014] No. 29) to address the weak foundation of pediatric clinical trials.[7] Subsequently, the "Technical Guidelines for Drug Clinical Trials in the Pediatric Population" ([2016] No. 48) was issued by the former China Food and Drug Administration (CFDA) to regulate pediatric trials at the technical operation level.[8] In addition to Chinese recommendations, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use E11 (R1) guideline, focusing on the clinical investigation of medical products in the pediatric population, has been implemented in China, and the E11A pediatric extrapolation guideline currently under public consultation addresses limiting the number of children needed for enrollment in clinical trials.[9,10] These encouraging policies have greatly promoted the process supervision and quality control of pediatric clinical trials and the development of child-friendly medicines.

In accordance with the requirements of the World Health Organization and international practices, the CFDA established the Registration and Information Disclosure Platform for Drug Clinical Trials in 2013 to implement trial registration and information publicity. The CFDA issued an announcement [2013] No. 28 regarding information registration for all industry-sponsored drug clinical trials approved by the CFDA and conducted in China, including phase I–IV drug trials and bioequivalence tests.[11] For trials initiated before 2013 without new drug applications, retrospective registration was needed. This official platform and corresponding measures have provided a solid foundation for analyzing the development trends in pediatric clinical trials testing new investigational drugs initiated by pharmaceutical companies in the past decade. In this study, the analysis of industry-sponsored pediatric clinical trials from 2013 to 2022 was conducted to support policy formulation and pipeline adjustment.

## METHODS

### Ethics approval

This study does not involve animal and patient experiments, and ethics approval and consent to participate are not applicable.

### Retrieval strategy and inclusion criteria

We conducted a cross-sectional study of trials registered from January 1, 2013, to December 31, 2022, on the Registration and Information Disclosure Platform for Drug Clinical Trials (www.chinadrugtrials.org.cn) (Figure 1). A total of 18 841 drug clinical trials were registered on this platform in the last decade. Due to retrospective

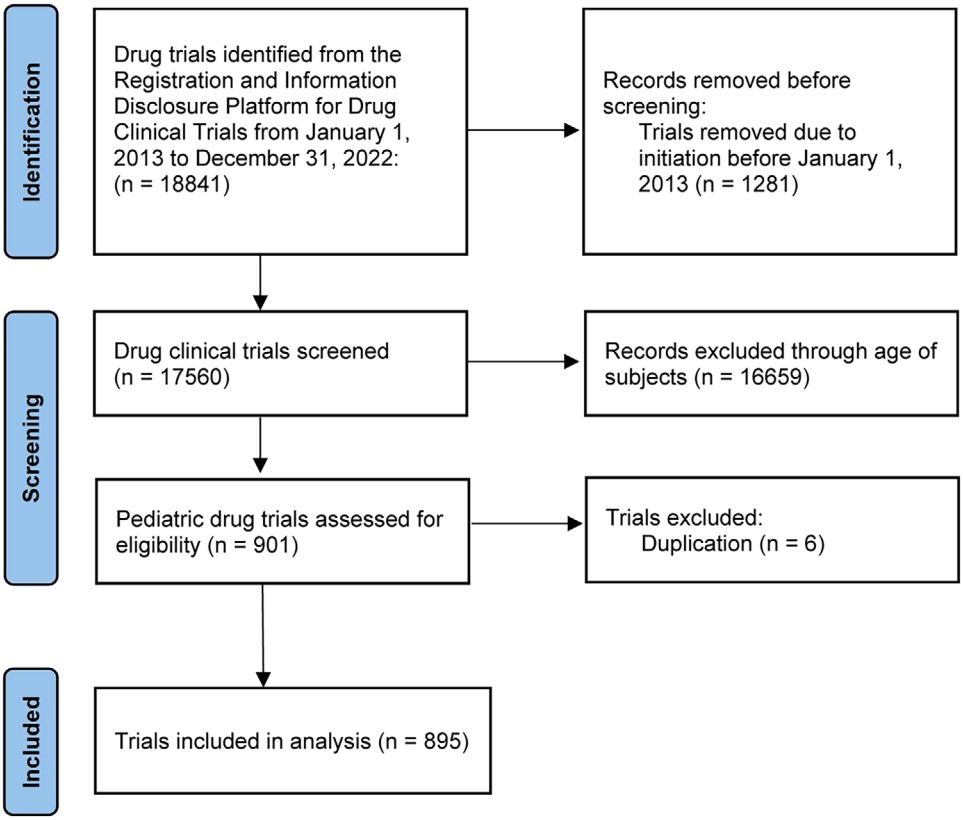


**FIGURE 1** Data processing flow diagram.

registration, early projects for supplementary registrations were included in 2013. We excluded drug trials initiated prior to January 1, 2013, according to the time of the first ethics review, leaving 17 560 trials. Using expert opinion and a manual review of the inclusion criteria of the studies, we roughly identified clinical trials that included subjects younger than 18 years of age and excluded those that did not include children. Two pediatric pharmacists specializing in pediatric clinical trials performed independent judgments (Yi Liu and Yuenan Qi), and a third expert (Jianmin Zhang) was invited to arbitrate when a disagreement arose. All searches were completed by Chang Liu in accordance with the retrieval strategy. To avoid information omission, we selected 20% of the trials from the excluded group ($n = 3332$) using a simple random sampling method and found that none included children. A total of 901 pediatric drug trials were identified. Duplicated trials with the same sponsor, drug, trial phase, and research content were eliminated by the two experts. In total, 895 pediatric drug clinical trials were included in the final analysis.

### Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics (version 21). For descriptive analyses, qualitative variables are presented as numbers and percentages. A simple regression model was used to analyze the 10-year trends in the numbers of initiated phase I–IV, rare disease, and different drug type trials. The year of the trial was defined as the date of the first ethics review. The indications for research drugs were coded using the eleventh edition of the International Classification of Diseases. The rare disease indications for drugs were analyzed with reference to the "First List of Rare Diseases" ([2018] No. 10) released in China by the National Health Commission of the People's Republic of China and other departments,[12,13] as well as the Orphanet database (https://www.orpha.net/) and the Genetic and Rare Diseases Information Center (https://rarediseases.info.nih.gov/diseases). A two-tailed $P < 0.05$ indicated statistical significance.

## RESULTS

### Time-related trends for initiated drug clinical trials in children

In China, a total of 895 pediatric drug trials were initiated by pharmaceutical enterprises from 2013 to 2022. The annual number of launched pediatric clinical trials increased over time, with an average annual growth rate of 12% ($P < 0.001$). Due to the impact of the coronavirus

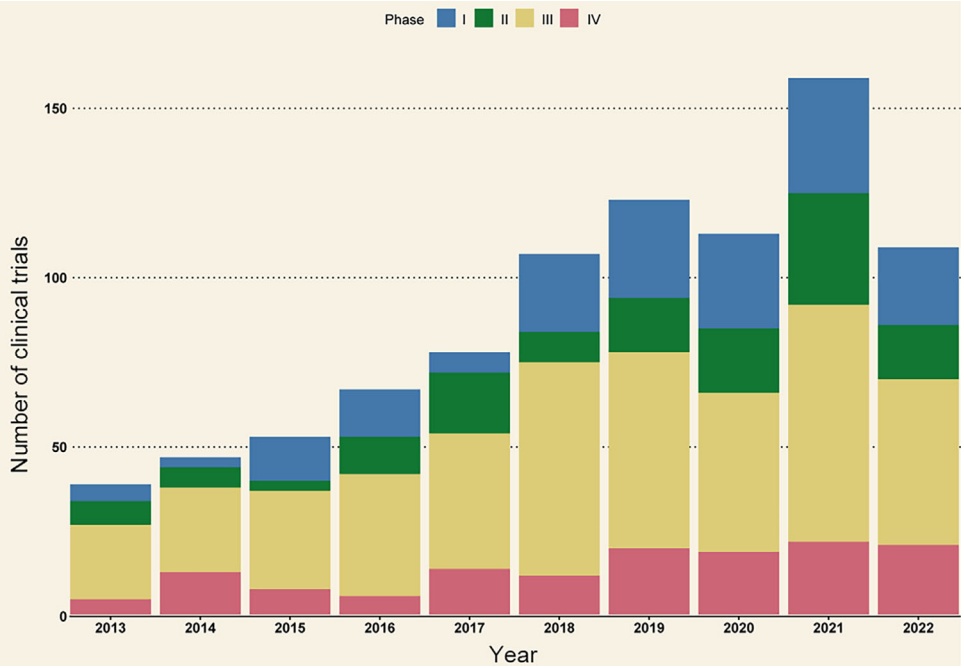


**FIGURE 2** The annual number of pediatric drug clinical trials in China from 2013 to 2022.

disease 2019, the growth trend for the number of clinical trials launched from 2020 to 2022 was relatively unstable, tending to first increase and then decrease (Figure 2). Phase III trials accounted for the highest proportion (49.1%, 439) of included trials, followed by phase I trials (19.9%, 178); phase II (15.4%, 138) and phase IV trials (15.6%, 140) accounted for similar proportions. The numbers of phase I–IV trials increased annually, with average annual growth rates of 18% ($P = 0.002$), 10% ($P = 0.012$), 9% ($P = 0.003$) and 17% ($P = 0.001$), respectively (Figure 2). Among these registered trials, a total of 736 (82.2%) were performed solely in China, and 159 (17.8%) were international multicenter trials. The number of domestic trials increased annually, with an average increase per year of 12% ($P < 0.001$). For international trials, the average annual growth rate was 14% ($P = 0.004$). A significant increase of 283% occurred in 2018, with 23 international trials launched (Figure 3).

## Trends for different tested drugs

Among the drug trials launched over the past decade, investigations of biological products accounted for the largest proportion of trials (67.4%, 603). Investigations of chemical drugs and traditional Chinese medicines (namely, natural medicines) accounted for 28.0% (251) and 4.6% (41), respectively, of the included trials. Biological product trials in children increased annually, with an average growth rate of 13% ($P < 0.001$), and most of the trials concentrated on vaccine development (60.9%, 367) and rare disease treatment (19.1%, 115). Pediatric clinical trials of chemical drugs exhibited an average annual increase of 11% ($P = 0.003$). Compared with 2017, in 2018, more pediatric clinical trials of chemical drugs were launched by enterprises, with a notable growth rate of 118%. However, the number of clinical trials in traditional Chinese medicine showed little annual change over the last decade. Most of the trials concerned respiratory system diseases (46.3%, 19) and infectious diseases (26.8%, 11). The trends for all tested drugs are shown in Figure 4.

Next, we further explored the total number and different types of drugs among clinical trials conducted in children (Figure S1). The total number of drugs in the clinical trials increased, with an average annual growth rate of 13% ($P < 0.001$). The numbers of biological products and chemical drugs in clinical phases increased annually, with average growth rates per annum of 14% ($P < 0.001$) and 11% ($P = 0.002$), respectively. The growth of traditional Chinese medicine research was relatively stable. Despite the upward trend for drugs in pediatric research, the quantity of drugs in the clinical trial phase is still low.

## Pediatric clinical trials and disease types

As shown in Table 1, vaccine studies ranked first among registered clinical trials involving children (41.0%, 367), mainly including trials of vaccines for influenza viruses (24.0%, 88), meningococcal (13.1%, 48), rabies (10.9%, 40), papillomavirus (9.5%, 35), pneumococcus (8.7%, 32), and others. There were 154 clinical trials for rare diseases, accounting for 17.2%, followed by respiratory system

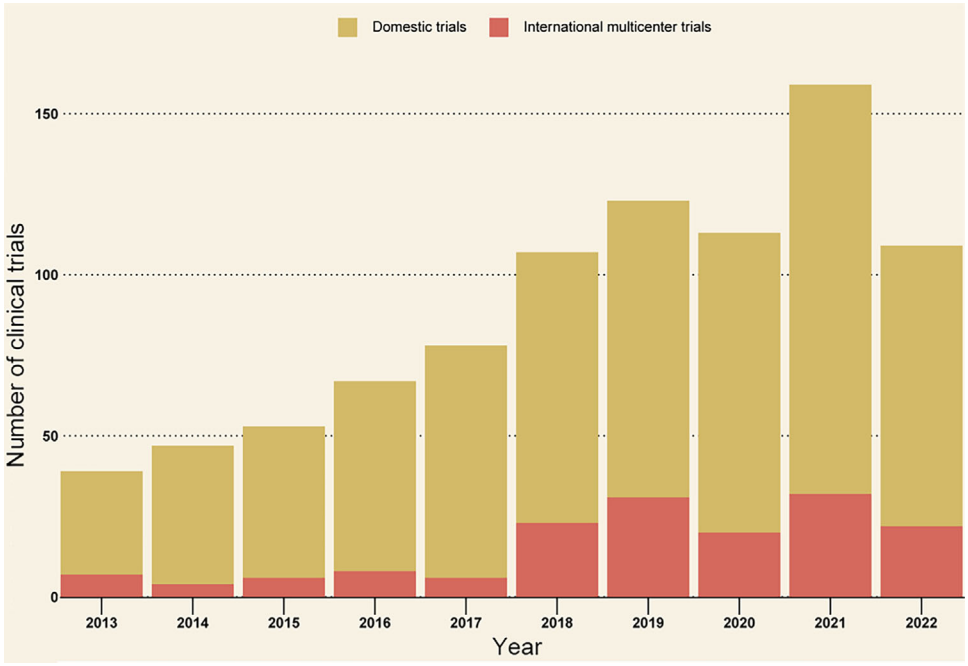


**FIGURE 3** The annual number of domestic and international pediatric drug clinical trials in China from 2013 to 2022.

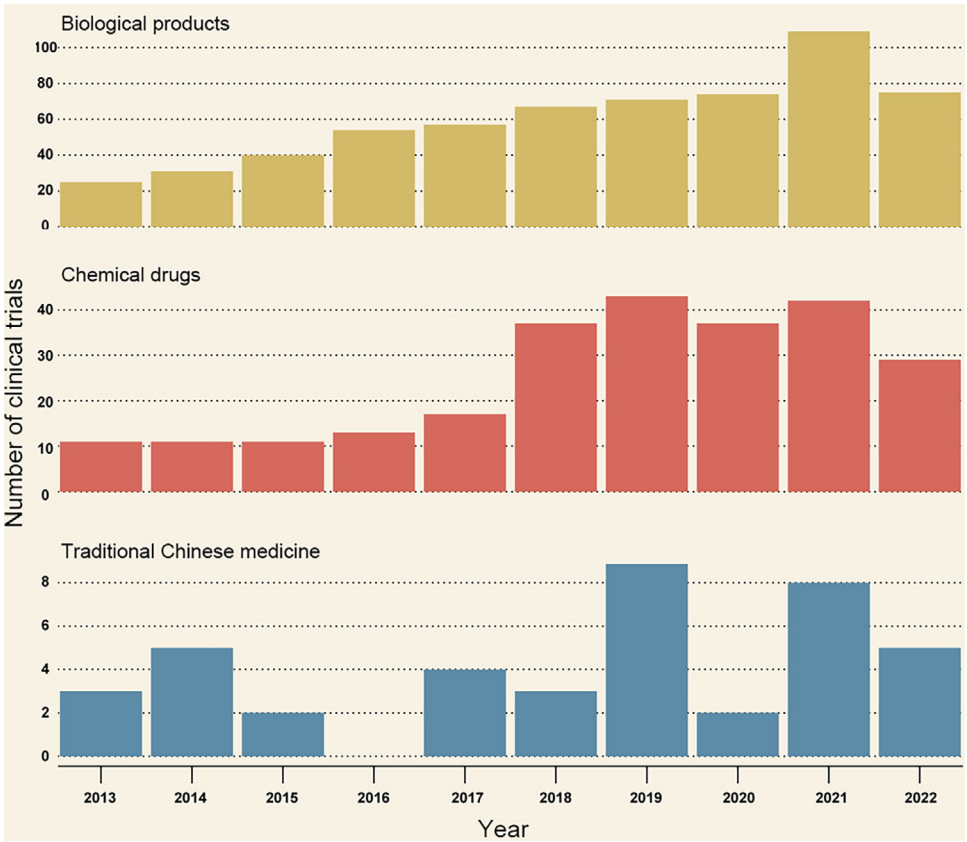


**FIGURE 4** The trends of pediatric drug clinical trials in China classified by drug type (biological products, chemical drugs, and traditional Chinese medicine) from 2013 to 2022.

**TABLE 1** Distribution of disease system among pediatric drug clinical trials

| Diseases | Number of trials, *n* (%) |
|---|---|
| Vaccine | 367 (41.0) |
| Rare diseases | 154 (17.2) |
| Diseases of the respiratory system | 65 (7.3) |
| Infectious diseases | 60 (6.7) |
| Neoplasms | 55 (6.1) |
| Endocrine, nutritional or metabolic diseases | 31 (3.5) |
| Diseases of the skin | 31 (3.5) |
| Diseases of the nervous system | 28 (3.1) |
| Diseases of the blood or blood-forming organs | 21 (2.3) |
| Diseases of the visual system | 15 (1.7) |
| Mental, behavioral or neurodevelopmental disorders | 14 (1.6) |
| Diseases of the digestive system | 12 (1.3) |
| Diseases of the immune system | 10 (1.1) |
| Others | 32 (3.6) |

diseases (7.3%, 65), infectious diseases (6.7%, 60), neoplasms (6.1%, 55), endocrine, nutritional or metabolic diseases (3.5%, 31), skin diseases (3.5%, 31), nervous system disorders (3.1%, 28), diseases of the blood or blood-forming organs (2.3%, 21), visual system illnesses (1.7%, 15), mental, behavioral or neurodevelopment disorders (1.6%, 14), digestive system diseases (1.3%, 12), and immune system diseases (1.1%, 10). The remaining trials investigated developmental anomalies, sedative anesthesia, and circulatory system diseases (3.6%, 32).

### Pediatric clinical trials of orphan drugs

Hemophilia was the most commonly identified type of orphan disease, with 71 (46.1%) trials, followed by juvenile idiopathic arthritis (6.5%, 10), spinal muscular atrophy (4.5%, 7), Duchenne muscular dystrophy (3.9%, 6), congenital fibrinogen deficiency (3.9%, 6), Gaucher's disease (3.2%, 5), and idiopathic short stature (2.6%, 4). The next most common indications were achondroplasia, Pompe disease, and Dravet syndrome, with three trials each. These were followed by inherited retinal degeneration, Fabry disease, atypical hemolytic uremic syndrome, Leber hereditary optic neuropathy, paroxysmal nocturnal hemoglobinuria, homozygous hypercholesterolemia, mucopolysaccharidosis, neurofibromatosis type 1 and multiple sclerosis, with two trials each. Autoimmune encephalitis and other rare diseases had the fewest trials, as shown in Figure 5, with one each. Pediatric clinical trials for rare diseases showed an upward trend, with an average rate of increase of 31% ($P < 0.001$). Gene therapy strategies are currently being applied for the treatment of rare diseases.[14] Thus, we further investigated gene therapies in China in the past decade. As shown in Table S1, therapeutic strategies, including RNA interference, antisense oligonucleotides, and adeno-associated viruses, were explored for the treatment of hemophilia, spinal muscular atrophy, Duchenne muscular dystrophy, inherited retinal degeneration, and Leber hereditary optic neuropathy.

### Geographical distribution of leading research centers

In general, the leading research centers for pediatric clinical trials were mainly located in North China (35.8%, 320), followed by East China (27.2%, 243), Central China (16.4%, 147) and South China (11.5%, 103), and the fewest research centers were in Northwest China (1.2%, 11), and Northeast China (0.8%, 7). These leading institutions covered 26 provincial administrative regions. The largest proportion of leading research centers was concentrated in Beijing (24.5%, 219), followed by Jiangsu Province (10.6%, 95), Henan Province (9.8%, 88), Shanghai (8.7%, 78), Tianjin (7.7%, 68), and Guangxi Autonomous Region (6.9%, 62). Zhejiang Province and Guangdong Province accounted for 5.1% (46) and 4.4% (40) of leading research units, respectively. The geographical distribution of leading institutions is shown in Table S2. We further explored the status of hospitals as leading research centers. Over the last decade, a total of 147 hospitals have conducted pediatric drug clinical trials as leading research centers. The top 10 hospitals that conducted the greatest number of trials as leading institutions are listed in Table S3.

## DISCUSSION

Pediatric drug accessibility has become a very noteworthy issue because of shortages and off-label uses. It is necessary to promote the development and trials of medications for children in China. In view of the lack of data on the current status of clinical trials involving Chinese children, in this study, the overall number of initiated trials, types of involved diseases and drugs, and geographic distribution imbalances of leading research centers that conducted sponsor-initiated pediatric trials were analyzed, and the overall trends for pediatric clinical trials in China over the past decade were assessed, providing a reference for clinical trial policymakers and industry stakeholders. The substantial increases in the number of initiated trials and participation in international multicenter trials suggest that progress was made from 2013 to 2022.

To encourage the development of innovative pediatric drugs, China has launched many regulatory initiatives that have led to a rapidly changing landscape.[15] As a result of substantial capacity building, a handful of drug candidates discovered in China have entered the global healthcare

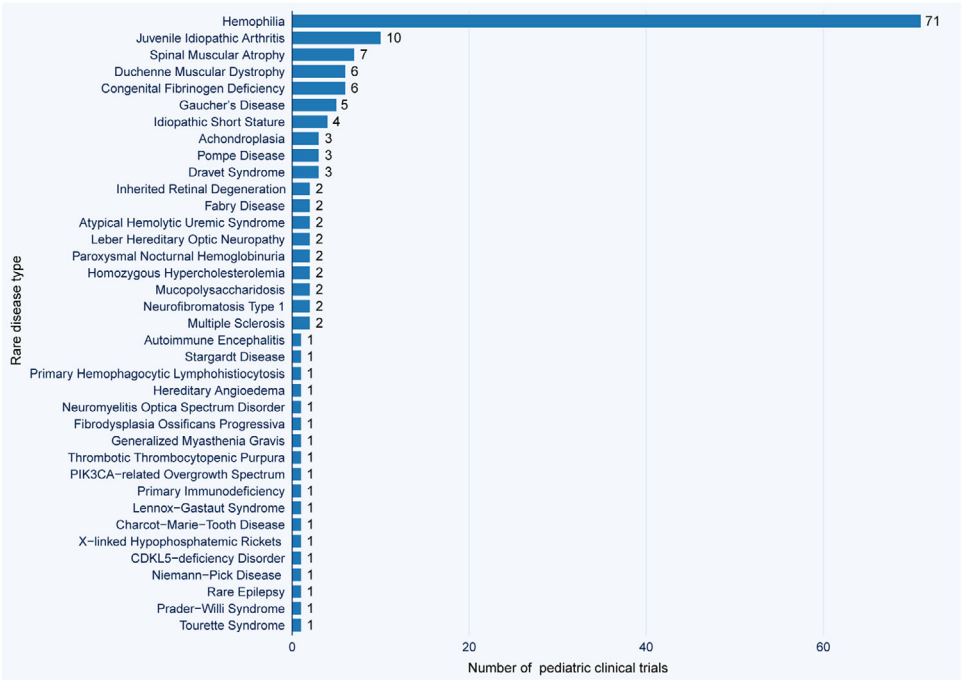


**FIGURE 5** Distribution of pediatric clinical trials for different types of rare diseases in China from 2013 to 2022.

system,[16] revealing the progress of pediatric drug development gained in the last decade and the contribution of Chinese biopharmaceutical companies to the global pipeline. Many companies are increasingly driven by the lure of an enormous Chinese drug market, instead of saving labor costs, and have set up operations in China.[16] The increasing involvement of international enterprises can result in cooperation with domestic service industries related to clinical trials. As the trends revealed in this study show, the number of clinical trials involving traditional Chinese medicine, the quintessence of China, has increased. Additionally, gene therapies for tumors and rare diseases have shown vigorous development. Biomedical enterprises should focus on the preclinical exploration and clinical research on new pediatric traditional Chinese medicines and gene therapies for children. The dynamic adjustment of development pipelines and enhanced investment, using the results of this study as a reference, can also drive the development of relevant enterprises. The gradual growth of Chinese pharmaceutical enterprises and progress in pediatric clinical trials have complemented each other over the years.

The filing system for clinical trial institutions released by the General Department of the State Drug Administration in 2019 requires sponsors to select medical or disease control institutions from within this system to perform drug clinical trials.[17] This measure favors access to pediatric clinical trial resources, better meets the needs of pediatric drug research and development, and is of great significance for encouraging pediatric drug innovation and promoting the healthy development of the pharmaceutical industry. However, geographically, clinical trial institutions are unevenly distributed. Cities with large populations or developed economies have the largest numbers of clinical trial institutions. Sponsors choose experienced hospitals as locations for the implementation of trials, providing a guarantee for the quality of the investigation. Unlike economically developed regions, less developed regions have a limited number of trial institutions due to software and hardware constraints. The relevant departments should intensify the publicity of the importance of clinical trials and promote hospital metrology accreditation to increase the number of trial institutions in these less developed regions. The enhanced qualification accreditation of clinical trial institutions can not only drive hospitals to keep up with the latest research frontiers but also promote the balanced allocation of medical resources to meet the increasing demand for pediatric drug development. The construction of medical alliances, including urban medical groups, county medical communities, cross-regional specialized medical alliances, and telemedicine collaboration networks, and the issuance of supporting policies can reduce disparities in clinical trial levels across regions and facilitate the coordinated development of different areas. In addition, related departments can promote the transfer of pharmaceutical industries to economically underdeveloped areas and strongly support cross-regional cooperation and co-construction. The

formation of pharmaceutical industrial parks can yield industrial agglomeration effects and improve the imbalance in regional medical and clinical research resources. The related departments can issue supportive policies to ameliorate the uneven geographic distribution of pediatric trials and construct expert committees to plan development pathways for pediatric medications, which can also help the related enterprises promote pediatric clinical research and achieve balanced development across the country.

Worldwide, there are more than 7000 rare diseases affecting over 300 million people.[18] Pediatric clinical trials on rare diseases face multiple challenges, including subject recruitment, limited knowledge of diseases, accurate diagnosis, and the choice of clinically relevant outcomes.[19] In recent years, the state has issued a series of documents to gradually address the challenges in the diagnosis and treatment of diseases and medication accessibility and affordability for individuals with rare diseases.[12,13] The supportive documents "Guidance Principles for Clinical Research and Development of Rare Disease Drugs" ([2021] No. 71)[20] and "Statistical Guidelines for Clinical Research of Rare Disease Drugs (pilot edition)" ([2022 No. 33])[21] released by the Center for Drug Evaluation of National Medical Products Administration have generated enthusiasm among pharmaceutical companies for developing orphan drugs. By the end of 2022, pediatric clinical trials of rare diseases were second only to investigations on vaccines. There are no clinical trials for many rare diseases in China, indicating unmet needs for these populations. Even for orphan drugs approved in the United States of America, the European Union, and Japan, the market availability in China is limited, and 22 orphan drugs for 14 rare diseases are unaffordable for most residents.[22] Among these unaffordable drugs, recombinant human coagulation factor VIIa for treating hemophilia, is the most unaffordable, followed by rituximab, sorafenib tosylate, imatinib, and bosentan.[22] It is necessary to provide a good development environment and supportive policies for pharmaceutical enterprises to improve the availability and affordability of orphan drugs.

In the process of orphan drug development, the enrollment of pediatric subjects is difficult. The number of potential subjects can be enhanced by leveraging the referral system from primary hospitals to superior hospitals and establishing a Chinese alliance for rare diseases. The construction of a national rare disease registry system and cooperative network would greatly facilitate the establishment of clinical cohorts for rare diseases based on the unique epidemiological characteristics of Chinese children. As the information level improves in hospitals, the patient digital screening system can be used to match potential subjects. It is also important for the government to issue supporting policies to encourage the authentication of hospitals in less developed areas as qualified clinical trial institutions to augment the probability of enrolling subjects. With the rapid development of decentralized clinical trials and online medical services, subject compliance can be improved, especially for patients with rare diseases living in less developed regions. In addition, as the key players in clinical trials, the institution and the sponsor can collaborate on academic projects. The bidirectional sharing of desensitized rare disease cohort data according to the unique characteristics of Chinese children can not only promote the further exploration and mapping of rare diseases in Chinese children but also facilitate research on and development of orphan drugs.

Using the trials registered on the mandatory registration platform, we systematically analyzed the overall landscape of pediatric clinical trials initiated by pharmaceutical enterprises in China from 2013 to 2022. However, our review has certain limitations. Although the trials registered on this official platform are audited by CFDA inspections, the relevant information is uploaded by sponsors, and some of the information is not completely standardized, which can lead to possible data deviations. Additionally, our review includes only trials initiated by pharmaceutical enterprises for new investigational drugs. Investigator-initiated pediatric trials registered in the ChiCTR database were not included. Furthermore, the initial year of the trials was defined as the year that the first ethics committee review took place, which may restrict comparisons with other reports using the time of online submission or first enrollment. Further analysis of the annual number of approved pediatric drugs in China would be valuable, but to our knowledge, no official database or report is available.

In conclusion, the data from 2013 to 2022 illustrate the gradual increase and progress in pediatric clinical trials initiated by pharmaceutical enterprises in China, suggesting the contribution of Chinese biopharmaceutical industries to the global pipeline. The large population base and increasingly improved capacity of Chinese pharmaceutical companies make China a favorable location for research on and the development of pediatric drugs. For diseases with epidemiology and outcomes unique to Chinese children and rare diseases, further exploration is needed. It is important to promote drug accessibility, affordability, development sustainability, and target accuracy. Additionally, further efforts should be made to balance the uneven geographical distribution of medical resources and satisfy the unmet needs of individuals with rare diseases through pediatric clinical trials.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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