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Pediatric Drugs Clinical Trials in China

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Pediatric Drugs Clinical Trials in China

Running title: Pediatric Clinical Trials in China

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Manuscript: 1089 words; References: 9; Figure: 2; Table: 2.

Abstract

Objective

Clinical trials of children's drugs are of great significance to rational drug use in children. However, clinical trials of pediatric drugs in China are facing complex challenges. At present, the investigation on the registration status of pediatric clinical trials in China is lacking, and relevant research is urgently needed to understand the impact of drug policy on pediatric drug development in China.

Methods

The advanced retrieval function is used to retrieve clinical trials data in the Clinical Trial.gov and Chinese Clinical Trial Registry databases. Fifteen key items were analyzed to describe trial characteristics.

Results

As of April 22, 2019, a total of 1388 clinical trials of pediatric drugs were registered in China. The number of pediatric drug trials registered grew steadily over time. Most clinical trials were post-marketing (n=800, 57.6%), single-center (n=1045, 75.3%), intervention studies (n=1161, 83.6%) without blinded methods (1169, 84.2%) and funded by non-profit organizations (n=838, 60.4%). The number of clinical trials for anti-infective drugs (n=291, 21.0%) and blood system drugs (n=198, 14.3%) is the largest.

Conclusion

Pediatric drugs clinical trials in China made a significant progress in recent years. Innovative method and trial design optimization should be encouraged

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4 to accelerate pediatric clinical research. Pharmaceutical companies need to be
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6 further stimulated to carry out more high-quality pediatric clinical trials with
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8 support of pediatric drug legislation.
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11 **Keywords:** Pediatrics, clinical trials, registration
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What is known about the subject?

(i) Clinical trials of children's drugs are of great significance to rational drug use in children

(ii) Starting from 2003, children were formally included in the scope of clinical trials in the Good Clinical Practice (GCP) in China.

What this study adds?

(i) Pediatric drugs clinical trials in China made a significant progress in recent years.

(ii) Most pediatric drugs clinical trials in China were post-marketing, single-center, intervention studies without blinded methods and funded by non-profit organizations.

(iii) The number of pediatric drugs clinical trials for anti-infective drugs and blood system drugs is the largest in China.

Introduction

The rational use of medicines in children is limited by the absence of scientific evidence and the off-label use of drugs is a critical issue in pediatric clinical practice, so the need for properly designed and conducted pediatric clinical trials has never been greater^{1,2}. Insufficient pediatric clinical trials increase the risk of adverse drug reactions in children³. Due to the scant information on pediatric prescriptions, clinicians often prescribe unauthorized indications or dosage forms of medicines for children^{4,5}. ADR monitoring data show that compared with 6.9% in adults, the ADR rate of children in China is 12.9%, of which 24.4% of neonates. According to World Health Organization (WHO) statistics in 2010, about 7.6 million children under the age of 5 die each year due to the lack of safe and effective drugs. The improper use of pediatric medicines will not only endanger children's health, but also bring misfortune to families and heavy burden to society.

Clinical trials are the golden standard for evaluating the safety and efficacy of drugs and producing evidence-based medical evidence. Registration of pediatric clinical trials is a preliminary plan for drug development in children. Pre-trial registration helps to reduce publication bias, selection bias, improve transparency of trials and make clinical trials conducted under public supervision, which is particularly important for the development of clinical trials for children⁶.

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4 The introduction of the Pediatric Regulation by the European Union, together
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6 with the renewal of the Pediatric Rule by the US Food and Drug Administration
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8 on the requirements for pediatric labeling made it mandatory for sponsors to
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10 develop drugs for the pediatric population and promotes the pediatric drug trials
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12 in Europe and US ^{7 8}. However, very little is known about the situation of
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14 pediatric drug trials in other countries, particularly in China, home to nearly 300
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16 millions children. In order to support the global research in pediatric drug
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18 development and clarify the specific Chinese characteristics of pediatric drugs
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20 trials, we analyzed the pediatric drug trials registered in China.
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26 27 28 **Methods**

29 30 31 **Design**

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34 We investigate the current status of pediatric clinical trials in China through the
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36 advanced retrieval functions of the Clinical Trial.gov (CTg) and Chinese Clinical
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38 Trial Registry (ChiCTR) databases. The data deadline is April 22, 2019. The
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40 key words of the ChiCTR are child, infant, enfant, newborn and adolescent (in
41
42 Chinese). Retrieve CTg qualification is Child (birth-18). The items enrolled into
43
44 the database include: registration number, year, mode of funding, type of
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46 disease, medicine type, research stage, research design, sample size, number
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48 of experimental groups, placebo group, blind method, implementation center,
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50 child-specific, newborn-specific and participant age.
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58 59 **Patient and Public Involvement**

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4 Patients or the public were not involved in the design, or conduct, or reporting,
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6 or dissemination of our research.
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9 10 **Results**

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12 Among all (n=34574) Chinese clinical trials registered in the CTg and ChiCTR,
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14 3368 trials (9.74%) involved the pediatric population. In CTg, the number of
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16 pediatric clinical trials in China accounts for 10.3% of the total number of
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18 pediatric clinical trials in the United States (n=2526/24488). A total of 1388
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20 clinical trials (4.01%) were pediatric drug trials, including 466 in CHICTR and
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22 922 in CTg.
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29 In these pediatric drug trials, 547 trials were designed specifically for children
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31 under the age of 18, including only 36 (0.259%) neonatal drug trials, while the
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33 other 841 trials involved both children and adults. The number of registered
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35 pediatric drugs clinical trials in China from 1983 to 2018 is shown in Figure 1.
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40 Most pediatric drug trials were classified as post-marketing study (n=800,
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42 57.6%), and were funded by non-profit organizations (n=838, 60.4%). The
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44 industry sponsored only 437 (31.5%) trials. Around two thirds (n=924) of trials
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46 were randomized and just about one eighth (n=168) involved a comparison with
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48 a placebo. The majority of trials were single centre studies (n=1045, 75.3%)
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50 and without blinded methods (n=1169, 84.2%). The number of interventional
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52 studies (1161) far exceeds that of observational studies (227). About two-thirds
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54 of clinical trials have a sample size of less than 300. The distribution of sample
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size is shown in Table 1.

According to the taxonomy of the Anatomical Therapeutic Chemical (ATC) Classification system, all ATC classes were represented in 1388 pediatric drug trials, with a predominant for drugs targeting blood and blood forming organs, and for systemic anti-infectives (Table 2). There were 93 pediatric drug trials including Chinese traditional medicine.

Discussions

In recent years, the Chinese government has adapted drug policy for children and paid more and more attention to the rational use of pediatric drugs and the development of pediatric clinical trials (Figure 2). Our results demonstrated for the first time the situation of pediatric drug trials in China. Consistent with the initiatives of promoting pediatric drug development in Europe and US, the pediatric drug trial in China made a significant progress after 2012.

Starting from 2003, children were formally included in the scope of clinical trials in the Good Clinical Practice (GCP) in China. This means that, like adults, children have the right to obtain evidence-based medical data for safe and effective treatment after clinical trials of new drugs under ethical and strict supervision. The development of pediatric clinical trials is conducive to protect children from invalid interventions. However, the proportion of children registered for clinical trials in China was 9.74% in this study, which was lower than that in Canada (22.4%), the United States (21.1%), the United Kingdom (18.5%), Japan (18.4%) and Germany (14.5%)⁹. Industry-sponsored trials are

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4 still limited in China and most of trials were still funded by public finding. This
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6 might be one obvious reason for the lack of significant increase in last few years.

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9 The pediatric drug legislation is urgently needed in China.

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11 This study shows that the proportion of observational research and
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13 interventional research is about 1:5, which shows that interventional research
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15 is more concerned and valued, and the content of observational research in
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17 design and implementation is broader and more complex. Single-center, non-
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19 blind research accounts for the majority of clinical trials,
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24 Furthermore, about one hundred trials involved Chinese traditional medicine.

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26 This is a real change compared to the traditional idea, which considered
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28 Chinese medicine as practical experiences. Indeed, the randomized clinical
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30 trials and longer-term safety evaluation are urgently needed to develop
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32 evidence-based therapy with Chinese traditional medicine in children.
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40 **Conclusions**

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42 Pediatric drugs clinical trials in China made a significant progress in recent
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44 years. Innovative method and trial design optimization should be encouraged
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46 to accelerate pediatric clinical research with joint efforts of regulator, scientist
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48 and clinicians. Pharmaceutical companies need to be further stimulated to carry
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50 out more high-quality clinical trials with support of pediatric drug legislation.
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58 **Author Contributions:** Prof Wei Zhao had full access to all of the data in the
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4 study and takes responsibility for the integrity of the data and the accuracy of
5
6 the data analysis. Study concept and design: Tian-You Wang, Wei Zhao;
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8 Acquisition, analysis, and interpretation of data: All authors; Drafting of the
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10 manuscript: Guo-Xiang Hao, Xiao-Xiao Yuan, Wei Zhao; Critical revision of the
11
12 manuscript: All authors. We plan to disseminate the results to study participants.
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29 (2018WSB19010).
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35 **Competing interests:** None.
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registration in the world based on ClinicalTrials. *Chin J Evid Based
Pediatr* 2016;11(1):3-7.

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Table 1 Sample size in pediatric drug clinical trials

sample size	No. of pediatric drug trials	Proportion (%)
0-100	538	38.7
101-200	264	19.0
201-300	144	10.4
301-400	90	6.5
401-500	54	3.9
501-1000	139	10.0
>1000	151	10.9
Unknown	8	0.6
Total	1388	100.0

Table 2 Classes of drugs in pediatric drug trials

Classes	No. of pediatric drug trials	Proportion (%)
Alimentary tract and metabolism	55	3.9
Blood and blood forming organs	198	14.3
Cardiovascular system	100	7.2
Dermatologicals	42	3.0
Genito urinary system and sex hormones	51	3.7
Systemic hormonal preparations, excl. sex hormones and insulins	72	5.2
Antiinfectives for systemic use	291	21.0
Antineoplastic and immunomodulating agents	158	11.4
Musculo-skeletal system	36	2.6
Nervous system	190	13.7
Antiparasitic products, insecticides and repellents	1	0.1
Respiratory system	124	8.9
Sensory organs	38	2.7
Various	32	2.3
Total	1388	100.0

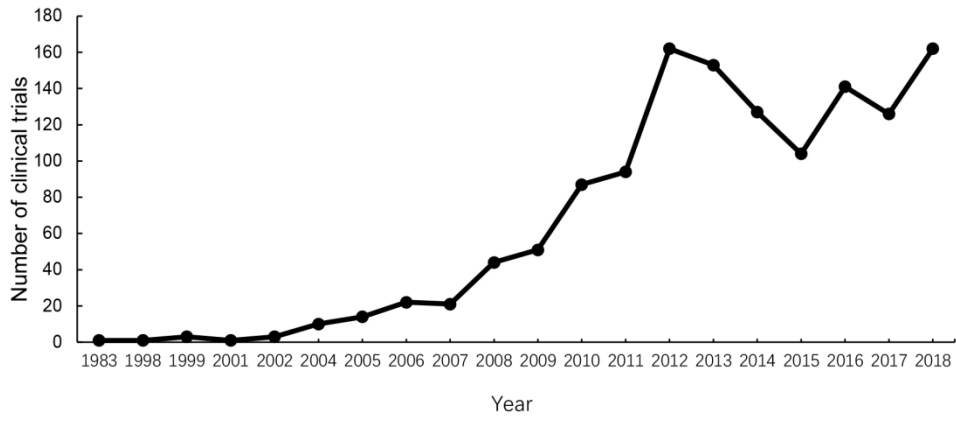
Figure legends

Figure 1 The number of registered pediatric drugs clinical trials in China from 1983 to 2018

Figure 2 Policies on Clinical Trials of Pediatric Drugs in China

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Figure 2 Policies on Clinical Trials of Pediatric Drugs in China

a: State Food and Drug Administration, SFDA (now namely National Medical Products Administration, NMPA); b: The State Council; c: Ministry of Health (now namely National Health Commission); d: National Health and Family Planning Commission, NHFPC (now namely National Health Commission); e: China Food and Drug Administration, CFDA (now namely NMPA); f: Ministry of Human Resources and Social Security; g: National Health Commission

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Running title: Pediatric Clinical Trials in China

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Abstract

Objective

Clinical trials of children's drugs are of great significance to rational drug use in children. However, pediatric drugs trials in China are facing complex challenges. At present, the investigation data on registration status of pediatric drug trials in China is still relatively lacking, and relevant research is urgently needed.

Methods

The advanced retrieval function is used to retrieve clinical trials data in the Clinical Trial.gov and Chinese Clinical Trial Registry databases in April 22, 2019. Fifteen key items were analyzed to describe trial characteristics, including: registration number, study start date (year), mode of funding, type of disease, medicine type, research stage, research design, sample size, number of experimental groups, placebo group, blind method, implementation center, child-specific, newborn-specific and participant age.

Results

A total of 1388 clinical trials of pediatric drugs conducted in China were registered. The number of pediatric drug trials grew steadily over time, from less than 20 per year before 2005 to more than 100 per year after 2012. Most clinical trials were post-marketing (n=800, 57.6%), single-center (n=1045, 75.3%), intervention studies (n=1161, 83.6%) without blinded methods (1169, 84.2%) and funded by non-profit organizations (n=838, 60.4%). The number of clinical trials for antineoplastic agents (n=254, 18.3%), antiinfectives (n=156,

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4 11.3%) and vaccines (n=154, 11.1%) is the largest.
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6 **Conclusion**

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9 Pediatric drug trials in China made a significant progress in recent years.
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11 Innovative method and trial design optimization should be encouraged to
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13 accelerate pediatric clinical research. Pharmaceutical companies need to be
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What is known about the subject?

(i) Clinical trials of children's drugs are of great significance to rational drug use in children

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Introduction

The rational use of medicines in children is limited by the absence of scientific evidence and the off-label use of drugs is a critical issue in pediatric clinical practice, so the need for properly designed and conducted pediatric clinical trials has never been greater^{1,2}. Insufficient pediatric clinical trials increase the risk of adverse drug reactions in children³. Due to the scant information on pediatric prescriptions, clinicians often prescribe unauthorized indications or dosage forms of medicines for children^{4,5}. Adverse drug reaction (ADR) monitoring data show that compared with 6.9% in adults, the ADR rate of children in China is 12.9%, of which 24.4% of neonates. According to World Health Organization (WHO) statistics in 2010, about 7.6 million children under the age of 5 die each year due to the lack of safe and effective drugs. The improper use of pediatric medicines will not only endanger children's health, but also bring misfortune to families and heavy burden to society.

Clinical trials are the golden standard for evaluating the safety and efficacy of drugs and producing evidence-based medical evidence. Clinical trial registration is to register the important information of the trial in the open clinical trial registration institution at the initial stage of the trial, so as to provide reliable information to the public, health practitioners, researchers and sponsors, and make the design and implementation of the clinical trial transparent. Pre-trial registration helps to reduce publication bias, selection bias, improve transparency of trials and make clinical trials conducted under public

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4 supervision, which is particularly important for the development of clinical trials
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6 for children⁶.
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10 The pediatric drugs trials in China mainly face two challenges, including the
11 support of adaptive policies and the application of new technologies and
12 methods. The introduction of the Pediatric Regulation by the European Union,
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14 together with the renewal of the Pediatric Rule by the US Food and Drug
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23 24 **Results**

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27 Among all (n=34574) Chinese clinical trials registered in the CTg and ChiCTR,
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29 3368 trials (9.74%) involved the pediatric population. In CTg, the number of
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31 pediatric clinical trials in China was 2526, compared with 24488 in the United
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33 States. A total of 1388 clinical trials (4.01%) were pediatric drug trials, including
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35 466 in CHICTR and 922 in CTg.
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41 In these pediatric drug trials, 547 trials were designed specifically for children
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43 under the age of 18, while the other 841 trials involved both children and adults.
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46 There are 148 clinical trials for infants (less than 1 year old), including 36 studies
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48 specifically for newborns. A total of 1048 clinical trials involve the age group of
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50 adolescents (from 12 to 18 years old), of which about four fifths included
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52 adolescents and adults. The number of registered pediatric drugs trials in China
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54 from 1983 to 2018 is shown in Figure 1.
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60 Most pediatric drug trials were classified as post-marketing study (n=800,

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4 57.6%), and were funded by non-profit organizations (n=838, 60.4%). The
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6 industry sponsored only 437 (31.5%) trials. Around two thirds (n=924) of trials
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8 were randomized and just about one eighth (n=168) involved a comparison with
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10 a placebo. The majority of trials were single centre studies (n=1045, 75.3%)
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12 and without blinded methods (n=1169, 84.2%). The number of interventional
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14 studies (1161) far exceeds that of observational studies (227). About two-thirds
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16 of clinical trials have a sample size of less than 300. The distribution of sample
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18 size is shown in Table 1.
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25 The drug classes in 1388 paediatric drug trials are shown in Table 2, among
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27 which the clinical trials for antineoplastic agents, antiinfectives and vaccines are
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29 the most. There were 93 pediatric drug trials including Chinese traditional
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31 medicine.
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36 Discussion

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39 In recent years, the Chinese government has adapted drug policy for children
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41 and paid more and more attention to the rational use of pediatric drugs and the
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43 development of pediatric clinical trials (Figure 2). Our results demonstrated for
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45 the first time the situation of pediatric drug trials in China. Consistent with the
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47 initiatives of promoting pediatric drug development in Europe and US, the
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49 pediatric drug trials in China made a significant progress after 2012.
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54 As reported, there were fewer pediatric randomized drug trials in developing
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56 countries than in developed countries in 1996-2002⁹. Especially in China, there
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58 are few pediatric drug trials. Starting from 2003, children were formally included
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4 in the scope of clinical trials in the Good Clinical Practice (GCP) in China. This
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6 means that, like adults, children have the right to obtain evidence-based
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8 medical data for safe and effective treatment after clinical trials of new drugs
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10 under ethical and strict supervision. The development of pediatric clinical trials
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12 is conducive to protect children from invalid interventions. However, the
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14 proportion of clinical trials registered for children in China was 9.74% in this
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16 study, which was lower than that in Canada (22.4%), the United States (21.1%),
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18 the United Kingdom (18.5%), Japan (18.4%) and Germany (14.5%)¹⁰. Industry-
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20 sponsored trials are still limited in China and most of trials were still funded by
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22 public finding. This might be one obvious reason for the lack of significant
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24 increase in last few years. The adaptive pediatric drug trials legislation is
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26 urgently needed in China to stimulate the enthusiasm of pharmaceutical
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28 companies.

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30 This study shows that the proportion of observational research and
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32 interventional research is about 1:5, which shows that interventional research
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34 is more concerned and valued, and the content of observational research in
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36 design and implementation is broader and more complex. In our study, the
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38 proportion of pediatric drug trials with more than 100 participants and 500
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40 participants was 61.3% and 20.9%, respectively, which is higher than 34% and
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42 7% of pediatric randomized controlled drug trials published in 2007¹¹. However,
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44 single-center, non-blind research accounts for the majority of clinical trials in
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46 China. At the same time, 60.1% of clinical trials recruited both adult and
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4 paediatric patients. Trials design needs to be further strengthened.
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7 The proportion of trials involving infants and newborns in China is lower than
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9 that in the pediatric randomized controlled drug trials published in 2007¹¹. In
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11 recent years, opportunistic sampling design, population pharmacokinetics
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13 model and model-based bridging approach have provided technical support for
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15 clinical trials of children's drugs^{12, 13, 14}. China has also launched the
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17 construction of a clinical evaluation technology platform for children's medicine,
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19 which will enhance the overall level of clinical research on children's medicine
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21 in China ¹⁵. However, how to apply these techniques and methods to trials
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23 design needs further exploration.
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30 Furthermore, about one hundred trials involved Chinese traditional medicine.
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32 This is a real change compared to the traditional idea, which considered
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34 Chinese medicine as practical experiences. Indeed, the randomized clinical
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36 trials and longer-term safety evaluation are urgently needed to develop
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38 evidence-based therapy with Chinese traditional medicine in children.
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45 **Conclusions**

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48 Pediatric drug trials in China made a significant progress in recent years.
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50 Innovative method and trial design optimization should be encouraged to
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52 accelerate pediatric clinical research with joint efforts of regulator, scientist and
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54 clinicians. Pharmaceutical companies need to be further stimulated to carry out
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56 more high-quality clinical trials with support of pediatric drug legislation.
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7 **Author Contributions:** Prof Wei Zhao had full access to all of the data in the
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9 study and takes responsibility for the integrity of the data and the accuracy of
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11 the data analysis. Study concept and design: Tian-You Wang, Wei Zhao;
12
13 Acquisition, analysis, and interpretation of data: All authors; Drafting of the
14
15 manuscript: Guo-Xiang Hao, Xiao-Xiao Yuan, Wei Zhao; Critical revision of the
16
17 manuscript: All authors. We plan to disseminate the results to study participants.
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Table 1 Sample sizes in pediatric drug trials

Sample size (participants (n))	No. of pediatric drug trials	Proportion (%)
0-100	538	38.7
101-200	264	19.0
201-300	144	10.4
301-400	90	6.5
401-500	54	3.9
501-1000	139	10.0
>1000	151	10.9
Unknown	8	0.6
Total	1388	100.0

Table 2 Classes of drugs in pediatric drug trials

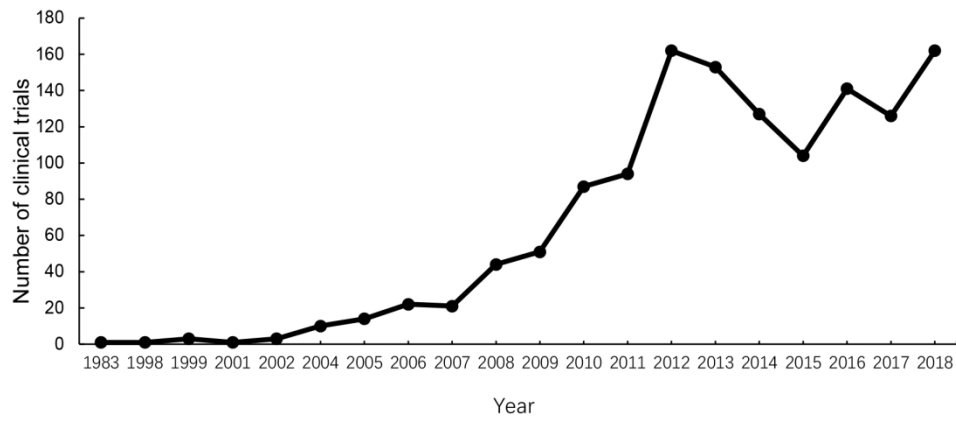
Classes	No. of trials	Proportion (%)
Antineoplastic agents	254	18.3
Antiinfectives	156	11.2
Vaccines	154	11.1
Anesthetics and analgesics	108	7.8
Anticoagulants, anticoagulants and hematopoietic agents	87	6.3
Immunosuppressants and glucocorticoids	81	5.8
Asthma drugs	50	3.6
Antihypertensive and cardiotoxic drugs	46	3.3
Dermatologicals	42	3.0
Vitamins, electrolyte solutions, nutrition and nutrient supplements	36	2.6
Antiepileptic drugs	33	2.4
Hormonal preparations	29	2.1
Diabetes medication	28	2.0
Antipsychotics	26	1.9
Drugs for pulmonary hypertension	21	1.5
Probiotic preparations	20	1.4
Ophthalmic drugs	20	1.4
Drugs for nerve injury repair and nervous system development	20	1.4
Others	177	12.8
Total	1388	100.0

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4 **Figure legends**

5 Figure 1 The number of registered pediatric drug trials in China from 1983 to
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7 2018
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9 Figure 2 Policies on pediatric drug trials in China
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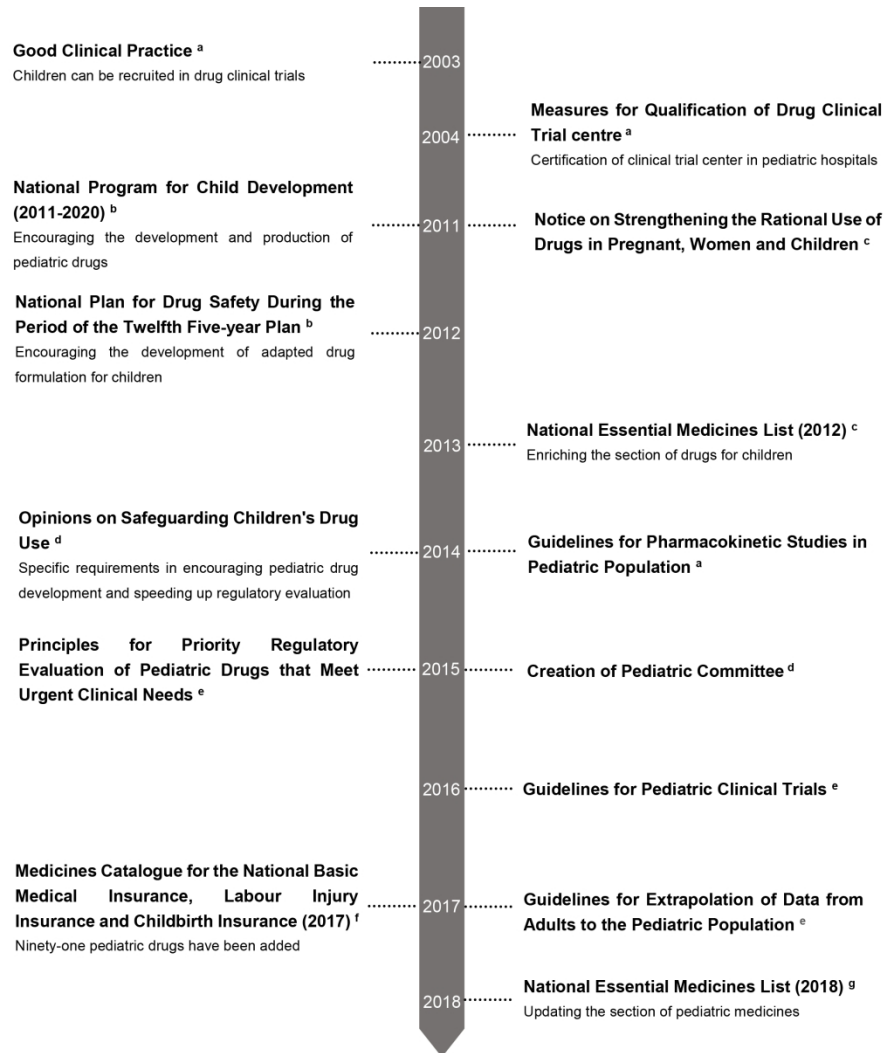


Figure 2 Policies on Clinical Trials of Pediatric Drugs in China

a: State Food and Drug Administration, SFDA (now namely National Medical Products Administration, NMPA); b: The State Council; c: Ministry of Health (now namely National Health Commission); d: National Health and Family Planning Commission, NHFPC (now namely National Health Commission); e: China Food and Drug Administration, CFDA (now namely NMPA); f: Ministry of Human Resources and Social Security; g: National Health Commission

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