BMJ Paediatrics Open

# Pediatric Drugs Clinical Trials in China



| | |
|---|---|
| Journal: | *BMJ Paediatrics Open* |
| Manuscript ID | bmjpo-2019-000618 |
| Article Type: | Original research |
| Date Submitted by the Author: | 29-Nov-2019 |
| Complete List of Authors: | Hao, Guo-xiang<br>Yuan, Xiao-xiao<br>Guo, Wei<br>Quan, Xi-Yu<br>Qi, Xue-Jie<br>Wang, Tian-You<br>Zhao, Wei; Shandong University, |
| Keywords: | Paediatric Practice, Evidence Based Medicine |
| | |

*I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.*

*The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.*

*Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.*

# Pediatric Drugs Clinical Trials in China

**Running title:** Pediatric Clinical Trials in China

Guo-Xiang Hao[1*], Xiao-Xiao Yuan[1*], Wei Guo[1], Xi-Yu Quan[1], Xue-Jie Qi[1], Tian-You Wang [2,3], Wei Zhao [1,4#]

* The first two authors contributed equally

1. Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Shandong University, Jinan, China

2. Beijing Key Laboratory of Pediatric Hematology Oncology, National Key Discipline of Pediatrics (Capital Medical University), Key Laboratory of Major Diseases in Children, Ministry of Education

3. Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

4. Department of Pharmacy, Shandong Provincial Qianfoshan Hospital, the First Hospital Affiliated with Shandong First Medical University, Jinan, China

Address for correspondence:

Prof Dr Wei Zhao

Department of Clinical Pharmacy, School of Pharmaceutical sciences, Shandong University, Jinan, 250012, China

Tel: 0086-531-88383308; fax: 0086-531-88383308

E-mail: zhao4wei2@hotmail.com

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

to accelerate pediatric clinical research. Pharmaceutical companies need to be further stimulated to carry out more high-quality pediatric clinical trials with support of pediatric drug legislation.

**Keywords:** Pediatrics, clinical trials, registration

**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 children [3]. 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 children[6].

The introduction of the Pediatric Regulation by the European Union, together with the renewal of the Pediatric Rule by the US Food and Drug Administration on the requirements for pediatric labeling made it mandatory for sponsors to develop drugs for the pediatric population and promotes the pediatric drug trials in Europe and US [7 8]. However, very little is known about the situation of pediatric drug trials in other countries, particularly in China, home to nearly 300 millions children. In order to support the global research in pediatric drug development and clarify the specific Chinese characteristics of pediatric drugs trials, we analyzed the pediatric drug trials registered in China.

## Methods

### Design

We investigate the current status of pediatric clinical trials in China through the advanced retrieval functions of the Clinical Trial. gov (CTg) and Chinese Clinical Trial Registry (ChiCTR) databases. The data deadline is April 22, 2019. The key words of the ChiCTR are child, infant, enfant, newborn and adolescent (in Chinese). Retrieve CTg qualification is Child (birth-18). The items enrolled into the database include: registration number, 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.

### Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research.

## Results

Among all (n=34574) Chinese clinical trials registered in the CTg and ChiCTR, 3368 trials (9.74%) involved the pediatric population. In CTg, the number of pediatric clinical trials in China accounts for 10.3% of the total number of pediatric clinical trials in the United States (n=2526/24488). A total of 1388 clinical trials (4.01%) were pediatric drug trials, including 466 in CHICTR and 922 in CTg.

In these pediatric drug trials, 547 trials were designed specifically for children under the age of 18, including only 36 (0.259%) neonatal drug trials, while the other 841 trials involved both children and adults. The number of registered pediatric drugs clinical trials in China from 1983 to 2018 is shown in Figure 1.

Most pediatric drug trials were classified as post-marketing study (n=800, 57.6%), and were funded by non-profit organizations (n=838, 60.4%). The industry sponsored only 437 (31.5%) trials. Around two thirds (n=924) of trials were randomized and just about one eighth (n=168) involved a comparison with a placebo. The majority of trials were single centre studies (n=1045, 75.3%) and without blinded methods (n=1169, 84.2%). The number of interventional studies (1161) far exceeds that of observational studies (227). About two-thirds of clinical trials have a sample size of less than 300. The distribution of sample

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

still limited in China and most of trials were still funded by public finding. This might be one obvious reason for the lack of significant increase in last few years. The pediatric drug legislation is urgently needed in China.

This study shows that the proportion of observational research and interventional research is about 1:5, which shows that interventional research is more concerned and valued, and the content of observational research in design and implementation is broader and more complex. Single-center, non-blind research accounts for the majority of clinical trials,

Furthermore, about one hundred trials involved Chinese traditional medicine. This is a real change compared to the traditional idea, which considered Chinese medicine as practical experiences. Indeed, the randomized clinical trials and longer-term safety evaluation are urgently needed to develop evidence-based therapy with Chinese traditional medicine in children.

## Conclusions

Pediatric drugs clinical trials in China made a significant progress in recent years. Innovative method and trial design optimization should be encouraged to accelerate pediatric clinical research with joint efforts of regulator, scientist and clinicians. Pharmaceutical companies need to be further stimulated to carry out more high-quality clinical trials with support of pediatric drug legislation.

**Author Contributions**: Prof Wei Zhao had full access to all of the data in the

study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Tian-You Wang, Wei Zhao; Acquisition, analysis, and interpretation of data: All authors; Drafting of the manuscript: Guo-Xiang Hao, Xiao-Xiao Yuan, Wei Zhao; Critical revision of the manuscript: All authors. We plan to disseminate the results to study participants.

**Funding:** This work is supported by National Science and Technology Major Projects for "Major New Drugs Innovation and Development" (2017ZX09304029-002), Young Taishan Scholars Program of Shandong Province, Qilu Young Scholars Program of Shandong University, National Natural Science Foundation of China (81503163), Medical and Health Science and Technology Development Program of Shandong Province (2018WSB19010).

**Competing interests:** None.

## References


1. Conroy S, Choonara I, Impicciatore P, et al. Survey of unlicensed and off label drug use in paediatric wards in European countries. European Network for Drug Investigation in Children. *BMJ* 2000;320(7227):79-82. doi: 10.1136/bmj.320.7227.79 [published Online First: 2000/01/22]
2. Davis JM, Connor EM, Wood AJ. The need for rigorous evidence on medication use in preterm infants: is it time for a neonatal rule? *JAMA* 2012;308(14):1435-6. doi: 10.1001/jama.2012.12883 [published Online First: 2012/10/11]
3. Gore R, Chugh P, Tripathi C, et al. Pediatric Off-Label and Unlicensed Drug Use and Its Implications. 2017;12(1):18-25.
4. Napoleone E. Children and ADRs (Adverse Drug Reactions). *Ital J Pediatr* 2010;36:4. doi: 10.1186/1824-7288-36-4 [published Online First: 2010/02/26]
5. Waisel DB. Moral responsibility to attain thorough pediatric drug labeling. *Paediatr Anaesth* 2009;19(10):989-93. doi: 10.1111/j.1460-9592.2009.03113.x [published Online First: 2009/08/08]
6. Pasquali SK, Lam WK, Chiswell K, et al. Status of the pediatric clinical trials enterprise: an analysis of the US ClinicalTrials.gov registry. *Pediatrics* 2012;130(5):e1269-77. doi: 10.1542/peds.2011-3565 [published Online First: 2012/10/03]
7. Pansieri C, Bonati M, Choonara I, et al. Neonatal drug trials: impact of EU and US paediatric regulations. *Arch Dis Child Fetal Neonatal Ed* 2014;99(5):F438. doi: 10.1136/archdischild-2013-305900 [published Online First: 2014/05/06]
8. Turner MA, Catapano M, Hirschfeld S, et al. Paediatric drug development: the impact of evolving regulations. *Adv Drug Deliv Rev* 2014;73:2-13. doi: 10.1016/j.addr.2014.02.003 [published Online First: 2014/02/22]
9. LI J, Yan K, Kong YT, et al. A cross-sectional study of children clinical trials

registration in the world based on ClinicalTrials. *Chin J Evid Based Pediatr* 2016;11(1):3-7.

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 |

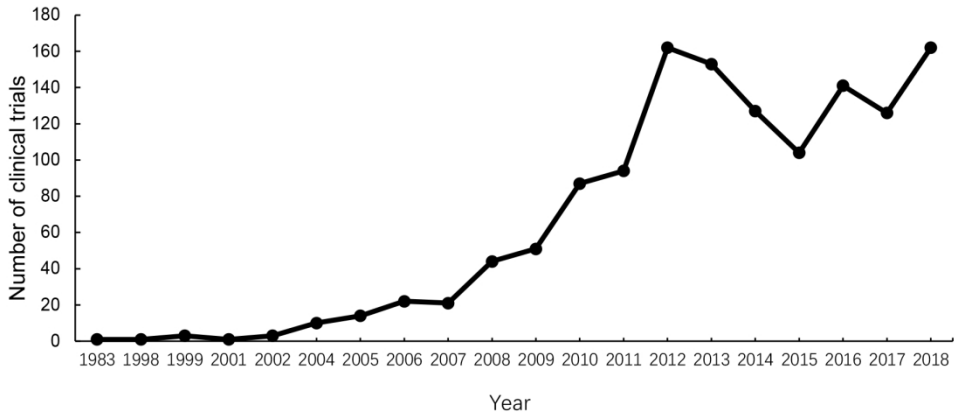
Table 2 Classes of drugs in pediatric drug trials

| 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




161x70mm (300 x 300 DPI)

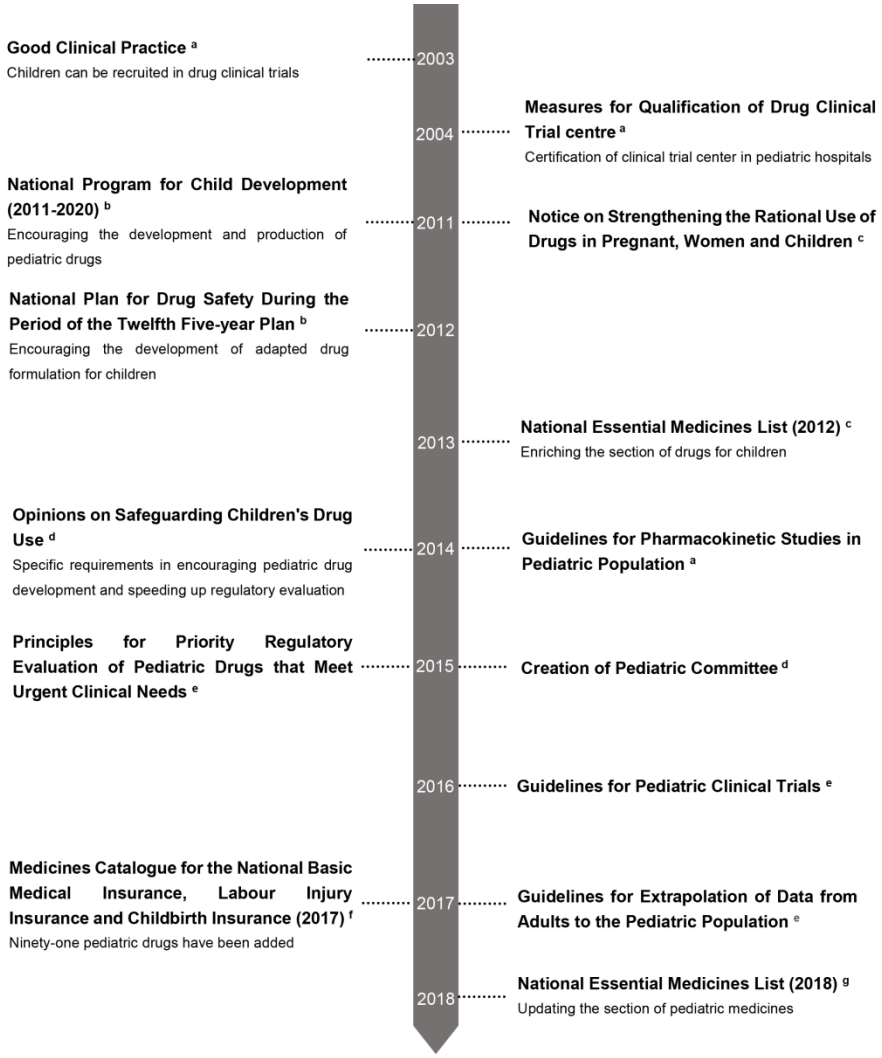



**Figure 2 Policies on Clinical Trials of Pediatric Drugs in China**

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

196x262mm (300 x 300 DPI)

BMJ Paediatrics Open

# Pediatric Drugs Trials in China



| | |
|---|---|
| Journal: | *BMJ Paediatrics Open* |
| Manuscript ID | bmjpo-2019-000618.R1 |
| Article Type: | Original research |
| Date Submitted by the Author: | 18-Jan-2020 |
| Complete List of Authors: | Hao, Guo-xiang<br>Yuan, Xiao-xiao<br>Guo, Wei<br>Quan, Xi-Yu<br>Qi, Xue-Jie<br>Wang, Tian-You<br>Zhao, Wei; Shandong University, |
| Keywords: | Paediatric Practice, Evidence Based Medicine |
| | |

*I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.*

*The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.*

*Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.*

# Pediatric Drugs Trials in China

**Running title:** Pediatric Clinical Trials in China

Guo-Xiang Hao[1*], Xiao-Xiao Yuan[1*], Wei Guo[1], Xi-Yu Quan[1], Xue-Jie Qi[1], Tian-You Wang [2,3], Wei Zhao [1,4#]

* The first two authors contributed equally

1. Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Shandong University, Jinan, China

2. Beijing Key Laboratory of Pediatric Hematology Oncology, National Key Discipline of Pediatrics (Capital Medical University), Key Laboratory of Major Diseases in Children, Ministry of Education

3. Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

4. Department of Pharmacy, Shandong Provincial Qianfoshan Hospital, the First Hospital Affiliated with Shandong First Medical University, Jinan, China

Address for correspondence:

Prof Dr Wei Zhao

Department of Clinical Pharmacy, School of Pharmaceutical sciences, Shandong University, Jinan, 250012, China

Tel: 0086-531-88383308; fax: 0086-531-88383308

E-mail: zhao4wei2@hotmail.com

Manuscript: 1371 words; References: 15; Figure: 2; Table: 2.

# 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,

11.3%) and vaccines (n=154, 11.1%) is the largest.

**Conclusion**

Pediatric drug trials in China made a significant progress in recent years. Innovative method and trial design optimization should be encouraged to accelerate pediatric clinical research. Pharmaceutical companies need to be further stimulated to carry out more high-quality pediatric clinical trials with support of pediatric drug legislation.

**Key words:** Pediatrics, clinical trials, registration

**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 drug trials in China made a significant progress in recent years.

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

(iii) The number of pediatric drug 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 children [3]. 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

supervision, which is particularly important for the development of clinical trials for children[6].

The pediatric drugs trials in China mainly face two challenges, including the support of adaptive policies and the application of new technologies and methods. The introduction of the Pediatric Regulation by the European Union, together with the renewal of the Pediatric Rule by the US Food and Drug Administration on the requirements for pediatric labeling made it mandatory for sponsors to develop drugs for the pediatric population and promotes the pediatric drug trials in Europe and US [7 8]. However, very little is known about the situation of pediatric drug trials in other countries, particularly in China, home to nearly 300 millions children. In order to support the global research in pediatric drug development and clarify the specific Chinese characteristics of pediatric drugs trials, we analyzed the pediatric drug trials registered to be conducted in China.

## Methods

### Design

We investigate the current status of pediatric clinical trials in China through the advanced retrieval functions of the Clinical Trial. gov (CTg) and Chinese Clinical Trial Registry (ChiCTR) databases. The data deadline is April 22, 2019. The key words of the ChiCTR are child, infant, newborn and adolescent (in Chinese). Retrieve CTg qualification is Child (birth-18). The items enrolled into the

database include: 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.

### Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research.

## Results

Among all (n=34574) Chinese clinical trials registered in the CTg and ChiCTR, 3368 trials (9.74%) involved the pediatric population. In CTg, the number of pediatric clinical trials in China was 2526, compared with 24488 in the United States. A total of 1388 clinical trials (4.01%) were pediatric drug trials, including 466 in CHICTR and 922 in CTg.

In these pediatric drug trials, 547 trials were designed specifically for children under the age of 18, while the other 841 trials involved both children and adults. There are 148 clinical trials for infants (less than 1 year old), including 36 studies specifically for newborns. A total of 1048 clinical trials involve the age group of adolescents (from 12 to 18 years old), of which about four fifths included adolescents and adults. The number of registered pediatric drugs trials in China from 1983 to 2018 is shown in Figure 1.

Most pediatric drug trials were classified as post-marketing study (n=800,

57.6%), and were funded by non-profit organizations (n=838, 60.4%). The industry sponsored only 437 (31.5%) trials. Around two thirds (n=924) of trials were randomized and just about one eighth (n=168) involved a comparison with a placebo. The majority of trials were single centre studies (n=1045, 75.3%) and without blinded methods (n=1169, 84.2%). The number of interventional studies (1161) far exceeds that of observational studies (227). About two-thirds of clinical trials have a sample size of less than 300. The distribution of sample size is shown in Table 1.

The drug classes in 1388 paediatric drug trials are shown in Table 2, among which the clinical trials for antineoplastic agents, antiinfectives and vaccines are the most. There were 93 pediatric drug trials including Chinese traditional medicine.

## Discussion

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 trials in China made a significant progress after 2012.

As reported, there were fewer pediatric randomized drug trials in developing countries than in developed countries in 1996-2002[9]. Especially in China, there are few pediatric drug trials. 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 clinical trials registered for children 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%)[10]. Industry-sponsored trials are still limited in China and most of trials were still funded by public finding. This might be one obvious reason for the lack of significant increase in last few years. The adaptive pediatric drug trials legislation is urgently needed in China to stimulate the enthusiasm of pharmaceutical companies.

This study shows that the proportion of observational research and interventional research is about 1:5, which shows that interventional research is more concerned and valued, and the content of observational research in design and implementation is broader and more complex. In our study, the proportion of pediatric drug trials with more than 100 participants and 500 participants was 61.3% and 20.9%, respectively, which is higher than 34% and 7% of pediatric randomized controlled drug trials published in 2007[11]. However, single-center, non-blind research accounts for the majority of clinical trials in China. At the same time, 60.1% of clinical trials recruited both adult and

paediatric patients. Trials design needs to be further strengthened.

The proportion of trials involving infants and newborns in China is lower than that in the pediatric randomized controlled drug trials published in 2007[11]. In recent years, opportunistic sampling design, population pharmacokinetics model and model-based bridging approach have provided technical support for clinical trials of children's drugs[12, 13, 14]. China has also launched the construction of a clinical evaluation technology platform for children's medicine, which will enhance the overall level of clinical research on children's medicine in China [15]. However, how to apply these techniques and methods to trials design needs further exploration.

Furthermore, about one hundred trials involved Chinese traditional medicine. This is a real change compared to the traditional idea, which considered Chinese medicine as practical experiences. Indeed, the randomized clinical trials and longer-term safety evaluation are urgently needed to develop evidence-based therapy with Chinese traditional medicine in children.

## Conclusions

Pediatric drug trials in China made a significant progress in recent years. Innovative method and trial design optimization should be encouraged to accelerate pediatric clinical research with joint efforts of regulator, scientist and clinicians. Pharmaceutical companies need to be further stimulated to carry out more high-quality clinical trials with support of pediatric drug legislation.

**Author Contributions**: Prof Wei Zhao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Tian-You Wang, Wei Zhao; Acquisition, analysis, and interpretation of data: All authors; Drafting of the manuscript: Guo-Xiang Hao, Xiao-Xiao Yuan, Wei Zhao; Critical revision of the manuscript: All authors. We plan to disseminate the results to study participants.

**Funding:** This work is supported by National Science and Technology Major Projects for "Major New Drugs Innovation and Development" (2017ZX09304029-002), Young Taishan Scholars Program of Shandong Province, Qilu Young Scholars Program of Shandong University, National Natural Science Foundation of China (81503163), Medical and Health Science and Technology Development Program of Shandong Province (2018WSB19010).

**Competing interests:** None.

## References


1. Conroy S, Choonara I, Impicciatore P, et al. Survey of unlicensed and off label drug use in paediatric wards in European countries. European Network for Drug Investigation in Children. *BMJ* 2000;320(7227):79-82. doi: 10.1136/bmj.320.7227.79 [published Online First: 2000/01/22]
2. Davis JM, Connor EM, Wood AJ. The need for rigorous evidence on medication use in preterm infants: is it time for a neonatal rule? *JAMA* 2012;308(14):1435-6. doi: 10.1001/jama.2012.12883 [published Online First: 2012/10/11]
3. Gore R, Chugh P, Tripathi C, et al. Pediatric Off-Label and Unlicensed Drug Use and Its Implications. 2017;12(1):18-25.
4. Napoleone E. Children and ADRs (Adverse Drug Reactions). *Ital J Pediatr* 2010;36:4. doi: 10.1186/1824-7288-36-4 [published Online First: 2010/02/26]
5. Waisel DB. Moral responsibility to attain thorough pediatric drug labeling. *Paediatr Anaesth* 2009;19(10):989-93. doi: 10.1111/j.1460-9592.2009.03113.x [published Online First: 2009/08/08]
6. Pasquali SK, Lam WK, Chiswell K, et al. Status of the pediatric clinical trials enterprise: an analysis of the US ClinicalTrials.gov registry. *Pediatrics* 2012;130(5):e1269-77. doi: 10.1542/peds.2011-3565 [published Online First: 2012/10/03]
7. Pansieri C, Bonati M, Choonara I, et al. Neonatal drug trials: impact of EU and US paediatric regulations. *Arch Dis Child Fetal Neonatal Ed* 2014;99(5):F438. doi: 10.1136/archdischild-2013-305900 [published Online First: 2014/05/06]
8. Turner MA, Catapano M, Hirschfeld S, et al. Paediatric drug development: the impact of evolving regulations. *Adv Drug Deliv Rev* 2014;73:2-13. doi: 10.1016/j.addr.2014.02.003 [published Online First: 2014/02/22]
9. Nor Aripin KN, Sammons HM, Choonara I. Published pediatric randomized drug trials in developing countries, 1996-2002. *Paediatr Drugs* 2010;12(2):99-103. doi: 10.2165/11316260-000000000-00000 [published Online First: 2010/03/12]
10. LI J, Yan K, Kong YT, et al. A cross-sectional study of children clinical trials

registration in the world based on ClinicalTrials. *Chin J Evid Based Pediatr* 2016;11(1):3-7.

11. Aripin KN, Choonara I, Sammons HM. A systematic review of paediatric randomised controlled drug trials published in 2007. *Arch Dis Child* 2010;95(6):469-73. doi: 10.1136/adc.2009.173591 [published Online First: 2010/05/27]
12. Leroux S, Turner MA, Guellec CB, et al. Pharmacokinetic Studies in Neonates: The Utility of an Opportunistic Sampling Design. *Clin Pharmacokinet* 2015;54(12):1273-85. doi: 10.1007/s40262-015-0291-1 [published Online First: 2015/06/13]
13. Hao GX, Huang X, Zhang DF, et al. Population pharmacokinetics of tacrolimus in children with nephrotic syndrome. *Br J Clin Pharmacol* 2018;84(8):1748-56. doi: 10.1111/bcp.13605 [published Online First: 2018/04/11]
14. Zhao W, Le Guellec C, Benjamin DK, Jr., et al. First dose in neonates: are juvenile mice, adults and in vitro-in silico data predictive of neonatal pharmacokinetics of fluconazole. *Clin Pharmacokinet* 2014;53(11):1005-18. doi: 10.1007/s40262-014-0169-7 [published Online First: 2014/08/27]
15. Wang XL, Zhang YJ. The Progress and Prospects of Pediatric Clinical Trial in China. *Journal of Pediatric Pharmacy* 2011;17(1):15-16. doi: 10.13407/j.cnki

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 |

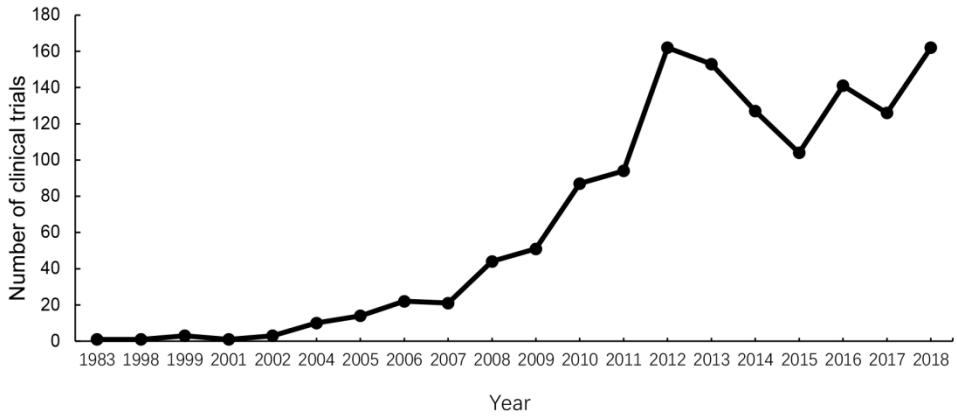
Table 2 Classes of drugs in pediatric drug trials

| 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 cardiotonic 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 |

## Figure legends

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

Figure 2 Policies on pediatric drug trials in China




161x70mm (300 x 300 DPI)

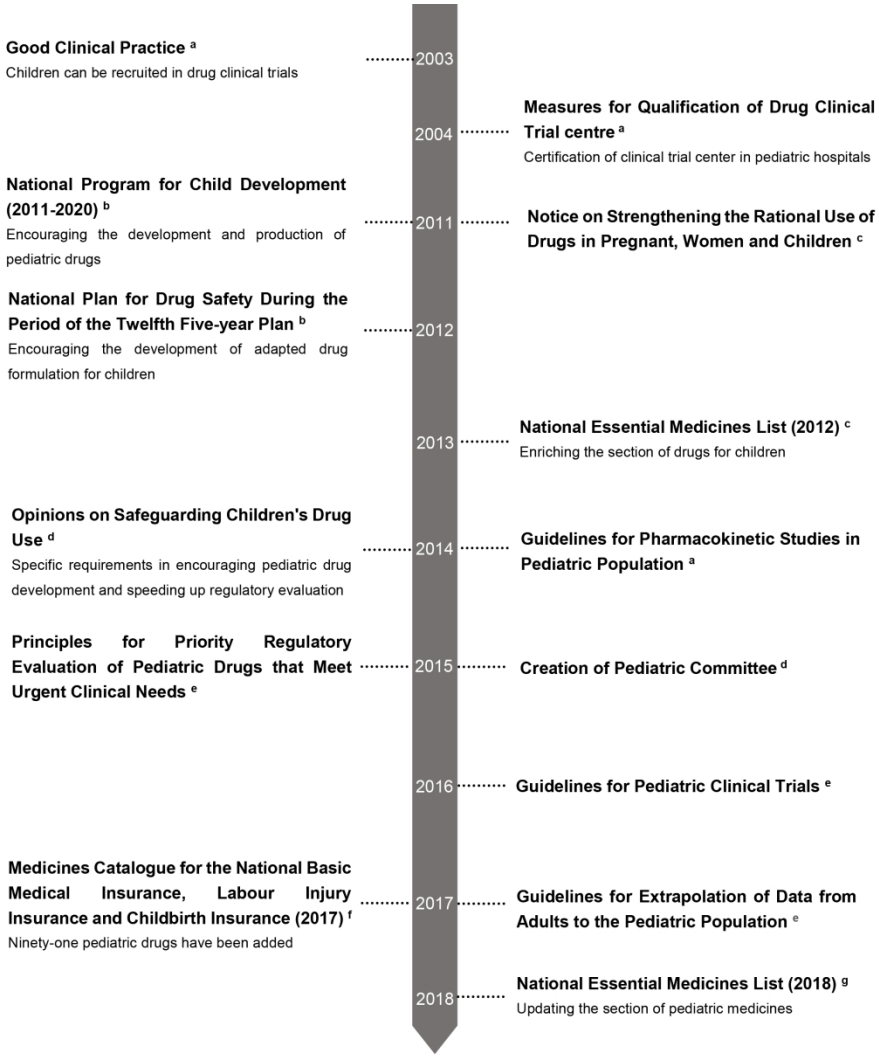



**Figure 2 Policies on Clinical Trials of Pediatric Drugs in China**

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

196x262mm (300 x 300 DPI)