PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Pediatric Drugs Trials in China
AUTHORS	Hao, Guo-xiang; Yuan, Xiao-xiao; Guo, Wei; Quan, Xi-Yu; Qi, Xue-Jie; Wang, Tian-You; Zhao, Wei

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Prof. Denis Verdasquera Corcho, MD, MSc, PhD Institution and Country: Full Professor and Researcher specialized in Hygiene, Epidemiology and Infectology National School of Public Health. Havana, Cuba Competing interests: None
REVIEW RETURNED	07-Dec-2019

GENERAL COMMENTS	The present study deals about the status of pediatric clinical trials in China conducted through a documental review. I consider that it is an article correctly designed and that fulfills with its fundamental objective. It would have been appropriate for the authors to specify the date on which these clinical trials were conducted and not only the deadline for their collection. In the same way, I consider that the authors should include the main challenges that China faces as a country today, and what the main lessons learned are during all these years.

REVIEWER	Reviewer name: Karel allegaert Institution and Country: KU Leuven, Belgium and Erasmus MC, Rotterdam, the Netherlands Competing interests: none, but I know and have published occasionally with the final author of the paper
REVIEW RETURNED	18-Dec-2019

GENERAL COMMENTS	I have read this paper with great interest. I value the effort, as the paper provides insights in the amount and the 'quality' or characteristics of the clinical studies in the field of pediatric drugs in china. Perhaps this second part can be further stressed throughout the paper. General comments Not sure if 'pediatric' drugs is an appropriate choice, as these drugs are not specific to pediatrics, but the clinical studies are, so I suggest to align the 'full title' to the short version of the title. Abstract: 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.= what does this mean ? Registration, but what about trends over time ?

	Introduction What do you mean with ‘registration of pediatric clinical trials is a preliminary plan for drug development in children’ ? The pattern that post marketing studies were funded by non-profit organizations is somewhat remarkable ? as one may anticipate that this is more a ‘industry’ task. Does this reflect off label related studies, supported by scientific societies and funding agencies ? Do you also have for the different age categories involved (cf table 1 and 2 concepts, we know the number of participants and the ATC, but can we also have an idea on the subpopulations, like newborns or adolescents ? Minor If possible with the word count restriction of the abstract, adding the 15 key words may be of additional benefit. ADR, first time in full in the paper ? You have searched two different registries, one more international, one more Chinese. Is there any difference in the study characteristics involved ? ‘we analysed the pediatric drug trials registered in china = registered to be conducted in china is perhaps more accurate ? Why ‘enfant’ ? as this is a French word ? (does the reflect the activities of the last author ?), please check You used the cut off age of 18 years, does this reflect the fact that is indeed the cut off for age in china to discriminate between ‘pediatrics’ and ‘adults’. How were studies handle including adolescents as part of adult studies ? Results, second sentence: Accounts for ? what do the authors mean ? do you mean that compared to the US ? In the intro you mention 2003, so has this resulted in changes in activities ? while only in the discussion, 2012 is raised. Please reconsider this, so that eg all ‘legal’ initiatives are mentioned in the intro ? Discussions, should read discussion

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

The present study deals about the status of pediatric clinical trials in China conducted through a documental review. I consider that it is an article correctly designed and that fulfills with its fundamental objective. It would have been appropriate for the authors to specify the date on which these clinical trials were conducted and not only the deadline for their collection. In the same way, I consider that the authors should include the main challenges that China faces as a country today, and what the main lessons learned are during all these years.

AUTHORS’ REPLY: Thanks for your review. We thank the reviewer for the positive evaluation of the review.

Sorry for the confusion. Concerning the date, the study start date (year) for each clinical trial has been collected in the original database and statistically displayed in Figure 1. In the Methods section, the expression of the item “year” enrolled into the database is changed to “study start date (year)”.

We agree with you. The pediatric drugs trials in China mainly face two challenges, including the support of adaptive policies and the application of new technologies and methods. We highlight in the introduction.

In recent years, opportunistic sampling design, population pharmacokinetics model and model-based bridging approach have provided technical support for pediatric drugs trials. China has also launched the construction of a clinical evaluation technology platform for pediatric drugs, which will enhance the overall level of clinical research on pediatric drugs in China. However, trials design needs to be further strengthened. At the same time, although in recent years, China has introduced some policies to encourage children's drug experiments, but it needs adaptive legislation to stimulate the enthusiasm of enterprises. We highlight in the discussion.

Reviewer: 2

I have read this paper with great interest. I value the effort, as the paper provides insights in the amount and the ‘quality’ or characteristics of the clinical studies in the field of pediatric drugs in china. Perhaps this second part can be further stressed throughout the paper.

AUTHORS’ REPLY: We thank the reviewer for the positive evaluation of the review. We agree with you. In the discussion, we strengthened the discussion on the quality or characteristics of the clinical studies in the field of pediatric drugs in China and compared it with the existing literature.

As reported, there were fewer pediatric randomized drug trials in developing countries than in developed countries in 1996-2002. Especially in China, there are few pediatric drug trials.

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. 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.

References

Nor Aripin KN, Sammons HM, Choonara I. Published pediatric randomized drug trials in developing countries, 1996-2002. Paediatr Drugs 2010;12(2):99-103.

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.

General comments

Not sure if ‘pediatric’ drugs is an appropriate choice, as these drugs are not specific to pediatrics, but the clinical studies are, so I suggest to align the ‘full title’ to the short version of the title.

AUTHORS’ REPLY: Thanks for your suggestions. Combining your and editor's suggestions, the title is changed to “Pediatric Drug Trials in China”.

Abstract:

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.= what does this mean ?

AUTHORS' REPLY: Sorry for the confusion. The sentence is changed to "At present, the investigation data on registration status of pediatric drug trials in China is still relatively lacking, and relevant research is urgently needed."

Registration, but what about trends over time ?

AUTHORS' REPLY: Thanks for your comments. The number of pediatric drug trials registered conducted in China grew steadily over time, from less than 20 per year before 2005 to more than 100 per year after 2012. Related content is added to the abstract.

Introduction

What do you mean with 'registration of pediatric clinical trials is a preliminary plan for drug development in children' ?

AUTHORS' REPLY: Sorry for the confusion. The sentence is changed to "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"

The pattern that post marketing studies were funded by non-profit organizations is somewhat remarkable ? as one may anticipate that this is more a 'industry' task. Does this reflect off label related studies, supported by scientific societies and funding agencies ?

AUTHORS' REPLY: Thanks for your comments. We agree with reviewer. Most pediatric drug trials were funded by non-profit organizations (n=838, 60.4%). In our opinion, this does reflect off label related studies supported by scientific societies and funding agencies. The adaptive pediatric drug trials legislation is urgently needed in China to stimulate the enthusiasm of pharmaceutical companies.

Do you also have for the different age categories involved (cf table 1 and 2 concepts, we know the number of participants and the ATC, but can we also have an idea on the subpopulations, like newborns or adolescents ?

AUTHORS' REPLY: Thanks for your suggestions. There are 148 clinical trials for infants (less than 1 year old), including 36 studies specifically for newborns. There were 1048 clinical trials involving the age group of adolescents (from 12 to 18 years old). Related content is added to the results section of the article.

Minor

If possible with the word count restriction of the abstract, adding the 15 key words may be of additional benefit.

AUTHORS' REPLY: Thanks for your suggestions. The key words are added in the abstract.

ADR, first time in full in the paper ?

AUTHORS' REPLY: Thanks for your comments. Corrected.

You have searched two different registries, one more international, one more Chinese. Is there any difference in the study characteristics involved ?

AUTHORS' REPLY: Thanks for your comments. We carefully compared the characteristics between the two registries, and the main contents of the two registries are similar.

'we analysed the pediatric drug trials registered in china = registered to be conducted in china is perhaps more accurate ?

AUTHORS' REPLY: Thanks for your suggestions. Corrected.

Why 'enfant' ? as this is a French word ? (does the reflect the activities of the last author ?), please check

AUTHORS' REPLY: Thanks for your comments. Sorry for the type error. Corrected

You used the cut off age of 18 years, does this reflect the fact that is indeed the cut off for age in china to discriminate between 'pediatrics' and 'adults'. How were studies handle including adolescents as part of adult studies ?

AUTHORS' REPLY: Thanks for your comments. In China, the age of 18 is not the boundary between pediatrics and adult medicine. This article chooses 18 years old as the demarcation line to follow the WHO definition of children. Our study found that four fifths of adolescent drug trials were conducted with adults.

Results, second sentence: Accounts for ? what do the authors mean ? do you mean that compared to the US ?

AUTHORS' REPLY: Thanks for your comments. This sentence is changed to: the number of pediatric clinical trial in China was 2526, compared with 24488 in the United States.

In the intro you mention 2003, so has this resulted in changes in activities ? while only in the discussion, 2012 is raised. Please reconsider this, so that eg all 'legal' initiatives are mentioned in the intro ?

AUTHORS' REPLY: Thanks for your comments. In 2003, the GCP only made it clear that clinical trials of the drug could be conducted in a child population. Until 2012, the introduction of a series of policies really promoted the development of pediatric drug trials.

Discussions, should read discussion

AUTHORS' REPLY: Thanks for your comments. Corrected.