Current Status and Trend of Clinical Development of Orphan Drugs in China

Ziling Xiang
Chongqing Medical University
Wengao Jiang
Chongqing Medical University
Bo Yan
Chongqing Medical University
Junhao Jiang
Chongqing Medical University
Hang Zheng (scnczh1979@sina.com)
School of Pharmacy, Chongqing Medical University, Chongqing, China https://orcid.org/0000-0003-2015-4990

Research

Keywords: Clinical trial, Rare disease, Orphan drugs, ChinaDrugTrials.org, NRDRS

Posted Date: September 23rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-915751/v1

Abstract

Background:

Rare diseases have been increasingly recognized as medical and healthy burden worldwide, a growing demand for the development of orphan drugs emerges subsequently. Therefore, it is of great interest for both the regulatory agency and pharmaceutical companies to keep tract on the clinical orphan drug development in China.

Objective and Method:

This study aims to reveal the current situation and trend of the clinical development of orphan drugs in China, based on the data collected from the Platform for Drug Clinical Trials and Information Registration （http://www.chinadrugtrials.org.cn）of China Food and Drug Administration, dating from 2013 to March 8, 2021.

Results:

A total of 246 clinical trials for orphan drugs are extracted from the Platform, covering 22 rare diseases and 90 drugs. Among the 22 rare diseases, 3 (14 %) have more than 50 trials each , 17 (77%) had less than10 trials, and 10 (46%) only with one trial. Among 90 orphan drugs, 60 (67%) were chemical drugs, and 30 (33 %) were biological products. In addition, international multi-center trials accounts for nearly 10% of the total trials. The number of the trials with the Data Monitoring Security Committee (DMC) is 25 (10%) and the number of the trials with the trial injury insurance for subjects is 154 (63%). Furthermore, more than half of the total trials are carried in east (333, 30%) and north China (298, 27%), whereas a small portion are in the northwest (62, 6%) and northeast china (45, 4%).

Conclusions:

The clinical development of orphan drugs for rare diseases in China has made some progress in the passing decades. However, a couple of critical issues still need to be addressed, such as unmet needs for some rare diseases, low coverage of insurance and DMC, and uneven distribution of medical resources for clinical researches. Recommendations are put forward accordingly, which can provide improvement goals for policy makers and stakeholders involved in drug development for rare diseases.

Introduction

There are more than 7000 rare diseases in the world, affecting more than 300 million people worldwide[1].The definition of rare diseases varies around the world. The WHO defines rare diseases with an incidence rate of 0.65‰ -1‰ among the general population. The United States defines rare diseases as those with fewer than 200,000 people per year (or less than 1/1500 of the population). The European Union defines the rare diseases as life-threatening or chronic progressive diseases with prevalence rates below 5/10000, while requiring special interventions. Japan defines rare diseases as those affecting less

than 50,000 people (or 1/2500 of the population)[2, 3]. In 2008, China released the first batch of rare diseases catalogue, involving 121 rare diseases, though a clear definition has not yet been given[4]. It is roughly estimated that there are about 20 million people with rare diseases in China[5]. Notably, the list of the 121 rare diseases do not include cancers with rare mutations.

The approved list of orphan drugs is limited due to many hurdles in the processes of drug development, including trial design, substrate recruitment, cost etc.. A study showed that a total of 133 orphan drugs covering 179 rare disease, were sold in the EU (ref.) in 2015. At the same time, in the United States, 415 orphan drugs (covering 521 rare diseases) have been approved[6]. In contrast, only a few orphan drugs were approved in China. For example, only 27 out of 60 FDA-approved orphan drugs were approved in China. Similarly, 8 out of 27 EMA-approved orphan drugs were approved in China. Among them, 14 drugs (52 %) were completely dependent on importation, 8 drugs (30 %) were manufactured domestically, while the remaining 5 drugs (19%) both can be produced domestically and imported [7].

An critical stage for drug development is to carry out clinical trials. Notably, clinical trials of rare diseases are even more difficult to implement due to multiple challenges, such as clinical trial design, patient recruitment, regulatory challenges, etc.[8, 9]. In recent years, research on clinical trials of rare diseases has attracted more and more attention. Through these studies, a lot of insightful analysis has been made on clinical trials of rare diseases, which provides useful reference for orphan drug development[10–12]. While most of these studies on rare diseases are based on databases such as the Clinical Trials.gov, analysis on clinical trials of rare diseases based on official databases in China are rare.

Understanding the current status of clinical trials of rare diseases are helpful to recognize and avoid the pitfalls during orphan drug development, and finally to make patients with rare diseases medically available. Therefore, this present study aims to explore the current status of clinical trials of rare diseases in China through specific data analysis based on the Platform for Drug Clinical Trials and Information Registration(http://www.chinadrugtrials.org.cn)of China Food and Drug Administration, Finally, suggestions are made to improve clinical development of orphan drug, which can be hopefully used as references for orphan drug R&D companies and policy makers in China.

Methods

1. Data source

Clinical trials data of orphan drugs were extracted from the Platform for Drug Clinical Trials and Information Registration(http://www.chinadrugtrials.org.cn)of China Food and Drug Administration which is an integrated platform for clinical trial registration and social publicity for drugs developed in China. The platform was initially launched on November 1st, 2012. And later on November 25th, 2013, an official version was launched independently. In 2013, the State Food and Drug Administration issued a bulletin on the drug clinical trial information platform in its official website, requiring that anyone who has obtained a clinical trial approval from the State Food and Drug Administration to carry out clinical trial in China

(including bioequivalence trials, phase I, II, III, IV trials, etc.), must register and publish the information on the platform, and the registration time limit should be specified.

2. Data collection

The first batch of rare diseases catalogue was jointly issued by the National Health and Health Commission, the Ministry of Science and Technology, the Ministry of Industry and Information Technology, the State Administration of Drugs and the State Administration of Traditional Chinese Medicine, which includes a total of 121 rare diseases. The name of 121 rare diseases, both as Chinese and English, were then used as the keywords to be searched in the platform. Diseases with multiple Chinese names will be searched with all the names available, with duplicated entries removed accordingly. In all, a total of 246 clinical trials of orphan drugs were extracted out from the database between 2013 and March 8th, 2021.

The clinical trial registration information extracted from the database includes, 1) basic information : registration number, initial publication date, participating agencies, etc. ; 2) management information: trial status, availability of data security monitoring committee (DMC) and trial injury insurance for subjects; 3) scientific information: tested drugs, drug types, trial design and scope (domestic trial or international multi-center trial), subject information, etc.. Abnormal or missing data will be corrected or imputed according to the original data.

3. Data analysis

Microsoft Excel (version 16.47) was used for data management. SPSS (version 24) was used for statistical analysis. Graphic figures were then created with ArcMap 10.2 and Excel. Basic statistical description of count data were presented as frequency and percentage. Chi-square test was used for the comparison between groups of enumeration data, and a p value less than 0.05 was used as the threshold of statistical significance.

Results

1. Number of clinical trials for different rare diseases

A total of 246 clinical trials of orphan drugs were extracted from the Platform for Drug Clinical Trials and Information Registration (http://www.chinadrugtrials.org.cn) from 2013 to March 8th, 2021, covering 22 rare diseases in the first list. Among the 22 rare diseases, 3 (14 %) have more than 50 trials each, 17 (77%) had less than 10 trials, and 10 (46%) only with one trial (Fig. 1). The top 5 most clinically studied diseases were Parkinson disease (young-onset, early-onset), hemophilia, homozygote hypercholesterolemia, idiopathic pulmonary fibrosis and multiple sclerosis. One clinical trial focuses on both multiple system atrophy and Parkinson disease (young-onset, early-onset). Thus it was counted twice for the rare diseases it covered, while only once to the total number of clinical trials for rare diseases.

2. Distribution of clinical trials in different years

Nearly half of the 246 clinical trials (110, 45%) are ‘other’ category (bioequivalence studies). In addition, there are 41 (17%) phase I trials, 20 (8%) phase II trials, 62 (25%) phase III trials and 12 (5%) phase IV trials.

Overall, the annual number of clinical trials of orphan drugs is on the rise from 2013 to 2020 (Mann-kedall test, $p = 0.0094$), with an average annual growth rate of 59%. A notable increase was identified in 2017, with 35 clinical trials launched, which is more than two fold increase as compared to 2016.

The proportion of phase I and phase II clinical trials showed a steady increase from 2018 to 2020, with an annual increase of 148% and 106%, respectively. While the proportion of “other” trials are gradually decreased, with an average change of 32% per year(Figure 2).

3. Drug types in clinical trials of rare diseases

Among the 246 clinical trials of orphan drugs, 170 were chemical drugs, accounting for 69%, and 76 were biological products, accounting for 31%. A total of 90 orphan drugs were tested in clinical trials between 2013 and March 8th, 2021. Among them, 60 (67%) were chemical drugs, and 30 (33 %) were biological products.

Since 2017, the proportion of clinical trials of chemical drugs gradually decreased, with an average annual decrease of 6%. And the proportion of biological products gradually increased, with an average change of 14% per year. In addition, the number of trials for chemical drugs has increased more than that for biological products (Fig. 3).

4. International *v.s* domestic of clinical trials of rare diseases

Domestic trials accounts for an absolute large proportion in the total number of clinical trials of rare diseases (n = 221, 90%), as compared to the international multi-center trials is (n = 25, 10%). The number of international multicenter trials reached a peak in 2020, accounting for 17.31% of all trials of rare diseases. However, the clinical trials of orphan drugs that are newly added each year are mainly from domestic trials (Figure 4).

5. Data Monitoring Security Committee & trial injury insurance

Among the 246 trials, only 25 (10%) had the Data Monitoring Security Committee (DMC).While 154 trials (63%) had trial injury insurance purchased for subjects. As shown in Table 1, 18 out 25 (72%) of the international multi-center trials had the data monitoring committee, which was significantly higher than that of the domestic trials (3%) ($\chi2 = 116.553$, $p < 0.001$, Table 1). Similarly, 24 out 25 (96%) of the international multi-center trials had trial injury insurance for subjects, which was significantly higher than that of the domestic trials (59 %) ($\chi2 = 11.718$, $p = 0.001$, Table 1).

Table 1
DMC and insurance status for clinical trials of orphan drugs

Project	international multicenter trials (N = 25)	Domestic trials (N = 221)	X2	P value
DMC				
yes	18(72%)	7(3%)	116.553	< 0.001
no	7	214		
insurance				
yes	24(96%)	130(59%)	11.718	0.001
no	1	91		

6. Geographical distribution of participating institutions in clinical trials of orphan drugs

From 2013 to March 8th, 2021, 227 clinical trial units were involved as the sites for clinical trials of orphan drugs in China, covering 31 provincial administrative regions. Peking union medical college hospital of Chinese Academy of Sciences has the highest number of clinical trials for rare diseases(n = 45), followed by Xiangya Hospital of Central South University (n = 40) and West China Hospital of Sichuan University (n = 39). In terms of the region, 189 trials were carried out in Beijing which is twice more than that in Shanghai (n = 84), and far more than that in other regions. In general, the highest number of clinical trial units of orphan drugs were located in east China (n = 73, 32%), followed by north China (n = 46, 11%), whereas the lowest in northwest China (n = 13, 6%). Consistently, the highest number of clinical trial of orphan drugs were also located in east China (n = 333, 30%), followed by north China (n = 298, 27%), whereas the lowest in northwest (n = 62, 6%) and northeast China (n = 45, 4%).

Discussion

This is the first comprehensive article on the status of rare disease clinical trials in China. The annual number of clinical trials indicates that certain progress has been made in the R & D of rare diseases in China from 2013 to 2020. Some results, such as the number of clinical trials for different rare diseases, the proportion of insurance and DMC, and the geographical distribution of participating institutions in clinical trials of orphan drugs, can be used as important guidelines for future research and development of rare disease drugs in China. However, there are still some shortcomings in the development, such as the limited number of clinical trials of some types of rare diseases, the low coverage of insurance and DMC in domestic trials, the uneven geographical distribution of participating institutions and the large gap in participation in clinical trials. These problems may provide future improvement goals for decision makers and stakeholders involved in drug development for rare diseases.

A total of 246 clinical trials of orphan drugs were extracted from the database, covering 22 diseases and 90 drugs. There is a large gap in the number of clinical trials among various rare diseases. Parkinson' s disease (young type, early-onset), hemophilia, homozygote familial hypercholesterolemia have the most clinical trials in operation. Data on incidence/prevalence of rare diseases in China are limited[13]. Thus, only a few data can be used to explore the comparison between the epidemiology of rare diseases and the number of clinical trials in China. Up to March 25th, 2021, the number of rare diseases registered on the National Rare Diseases Registry System of China (NRDRS) has reached 63438, the top 3 of which are hemophilia, rare pulmonary hypertension and Duchenne/Becker muscular dystrophy, followed by spinocerebellar ataxia, pituitary adenoma, autosomal dominant polycystic kidney disease, primary dystonia, myasthenia gravis, Alport syndrome, and early onset muscular dystrophy. Among the top 10 rare diseases in the number of clinical trials, the number of actual registered cases of 6 rare diseases ranked in the top 26. In contrast, even though the reported cases of familial hypercholesterolemia and Gaucher's disease are lower, ranking 122nd and 74th, but they attracted a great portion of clinical trials. In addition, 98 out of the 121 rare diseases need drug treatment [14]. Among them, there are only one clinical trial for 10 rare diseases, and the remaining 77 clinical trials for rare diseases have not been carried out in China,indicating an unmet and demanding needs for these patients. Notably, this situation also occurs in other countries. For example, it has been shown that the EU does not have orphan products for certain rare diseases[6]. And the orphan drugs under clinical trials cannot fully meet the clinical needs in the future.

Another critical issue is that a great portion of clinical trials covers only a small number of orphan drugs. Many pharmaceutical companies invest money in the same drug, especially in the clinical trials of Parkinson' s disease and homozygous familial hypercholesterolemia. Furthermore, bioequivalence studies account for a great portion and innovative drugs are rare. This phenomenon is also a reflection of the lack of innovation in China ' s pharmaceutical industry. The situation of lacking treatable drugs for some rare diseases in China will not be alleviated in the near future. However, available treatment might be obtained from imported drugs for these rare diseases.

The gradual growth of the annual number of clinical trials indicates that some progress has been made in the R & D of orphan drugs in China from 2013 to 2020. A steady growth can be observed for the number of orphan drug clinical trials since 2013, especially since 2016, the total amount has increased rapidly, benefiting from the reform of drug review and approval system in China, and the promotion policy for the research and development of orphan drugs [151617].

In recent years, the number of phase I and II clinical trials has increased significantly, consistently with an increase of orphan drugs at pre-clinical stage. Although 45 % of clinical trials are bioequivalence trials, its proportion is gradually decreasing each year. Many pharmaceutical companies tend to develop generic drugs, instead of original drugs, mainly due to the following reasons. First of all, there is a lack of epidemiological data on rare diseases in China, and the number of patients and market capacity, which increase the risk of R & D in companies. Secondly, since the pool of eligible patients of rare diseases is quite small, it is also a problem whether enterprises can make a profit of the new drug in a certain period of time. The development of new drug from laboratory to clinic is an extremely risky, and time- and money-

consuming business. Finally, the development of generic drugs is also encouraged by the government while supporting the development of innovative drugs. In October 2019, the National Health Commission issued the first batch of 33' National Encouraging Catalogs of Imitation Drugs', including 6 orphan drugs for the treatment of 4 rare diseases[18].

The clinical trials of rare diseases in China are mainly domestic trials. The international multicenter trials only accounts for a small portion, and are mainly carried out by global pharmaceutical companies. While many rare disease phase III clinical trials are international multicenter studies, it is also encouraged that the international multicenter trials should not be constrained in phase III clinical trials, but also expanded to other phases of clinical trials.

The proportion of DMC and trial injury insurance for subjects in international multicenter trials were significantly higher than those in domestic trials (DMC, 72 % *v.s* 3 %; Insurance, 96 % *v.s* 59%). A study showed that, the appointment of data monitoring committee (DMC) was more common in rare disease trials as compared other clinical trials (53% *v.s* 41 %) [19]. Patients with rare diseases are a special and vulnerable group, so clinical trials involving these patients should be carried out with more caution. Trial insurance is highly recommended to be purchased to not only protect the rights and interests of subjects, but also these of enterprises. Apparently, the Chinese enterprises have not yet realized its importance. Although the number of orphan drug clinical trials in China is increasing, the insurance coverage is quite low, partially due to the incomplete clinical trial insurance system in China..

The extent of participation in orphan drug clinical trials varies greatly among different hospitals. Most of the institutions participating in rare disease clinical trials are tertiary hospitals with strong research background. Peking Union Medical College Hospital has the highest number of clinical trials, and the hospitals in Beijing have the largest portion of orphan drug clinical trials. In 2019, Peking union medical college hospital lead in the establishment of a rare disease diagnosis and treatment cooperation network in China. In addition, Peking Union Medical College hospital is also responsible for building a national rare disease registration research platform. Beijing takes a leading role in guiding the development of rare diseases in China, which is reflected by its largest share of orphan drug clinical trials (twice more than that of Shanghai) in China.

The number of orphan drug clinical trials varies greatly in different regions in China. Further analysis showed that the regions with highest number of orphan drug clinical trials were consistent with the regions with highest number of registered cases on NRDRS. As of March 25th ,2021, Shandong had the largest number of registered cases on NRDRS, followed by Sichuan, Hebei, Zhejiang, Beijing, Henan and Jiangsu. In general, orphan drug clinical trials in China are mainly distributed in the developed regions, such as the northern and eastern China. However, this also reflects some problems. The distribution of medical resources for rare disease clinical research in China is quite uneven, which is partially due to the leading role of large clinical trial units required by the government [20]. In the future, the government should also consider the problem of regional imbalance, so that more institutions, greater areas can be involved in clinical trials for orphan drug.

To solve these problems, we should first pay attention to the unmet needs of the research and development of orphan drugs and promote drug development in related diseases. Secondly, we need to improve the rare disease clinical trial registration database and rare disease diagnosis and treatment cooperation network. Thirdly, a systematic, comprehensive and timely rare disease clinical trial recruitment platform, new recruitment methods, and international collaboration are expected to be applied to promote rare disease clinical trial recruitment. Besides, we should improve the coverage of insurance and DMC in rare disease clinical trials to provide protection for R & D enterprises and subjects. Finally, we should encourage the participation and improve the quality of orphan drug clinical trials in medical institutions across a wider region in China.

Limitation

The limitation of the current study is listed below. Firstly, this database is input by enterprises themselves, and there is the possibility of missing or mis-recording of data. In addition, part of the input is not standardized, which can possibly result in potential data deviation. Secondly, this study collected orphan drug clinical trials data solely registered on the drug clinical trial registration and information disclosure platform, and did not include clinical trials initiated by investigators. Thirdly, only 121 rare diseases were retrieved, which did not take into account of clinical trials for other rare diseases.

Conclusion

In summary, the current situation and development trend of clinical trials of orphan drugs in China were systematically analyzed for the first time based on the registration system of rare diseases in China. From 2013 to March 8th, 2021, the research and development of orphan drugs in China has made some progress, but there are still many problems, such as the unmet needs for some rare diseases, the low coverage of insurance and DMC, and the uneven distribution of medical resources for clinical research of rare diseases. Recommendations are put forward accordingly to the problems. It is hoped that pharmaceutical companies can further improve their innovation ability. The government should improve the legal system concerning to rare diseases in a more timely manner, and put forward certain policies according to the situation, so as to provide protection for patients with rare diseases.

Declarations

Acknowledgements

The authors would like to thank the contribution of Hong Yang for reviewing the manuscript and providing her comments.

Authors' Contribution

Ziling Xiang wrote the manuscript; all authors designed the research; Ziling Xiang and Hang Zheng performed the research; Ziling Xiang analyzed the data.

Funding

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available as they contain confidencial commercial information, Limited information may be available from the corresponding author upon request but will be reviewed to protect proprietary information.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Wakap SN, Lambert DM, Olry A, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *European Journal of Human Genetics* Feb. 2020;28(2):165–73. doi:10.1038/s41431-019-0508-0.
2. Melnikova I. Rare diseases and orphan drugs. Editorial Material. *Nat Rev Drug Discov* Apr. 2012;11(4):267–8. doi:10.1038/nrd3654.
3. Zhao H, Cui Y, Zhou X, et al. Study and analysis of the state of rare disease research in Shandong Province, China. *Intractable & rare diseases research*. 2012-Nov. 2012;1(4):161–6. doi:10.5582/irdr.2012.v1.4.161.
4. Notice on the first official list of rare diseases (in Chinese). https://www.nhc.gov.cn/yzygj/s7659/201806/393a9a37f39c4b458d6e830f40a4bb99.shtml. Accessed 10 Aug 2021.
5. Yan X, Dong D, He S, Webster C. Examining Trans-Provincial Diagnosis of Rare Diseases in China: The Importance of Healthcare Resource Distribution and Patient Mobility. *Sustainability* Jul. 2020;12(13):5444. doi:10.3390/su12135444.
6. Giannuzzi V, Conte R, Landi A, et al. Orphan medicinal products in Europe and United States to cover needs of patients with rare diseases: an increased common effort is to be foreseen. *Orphanet Journal of Rare Diseases* Apr. 2017;3:1264. doi:10.1186/s13023-017-0617-1.
7. Lihua Liu JZ. Xiaochun Zuo and Lin Lin. Fundamental considerations in the clinical review of the registration application for the treatment of rare diseases. Chinese Journal of Clinical Pharmacology.

2018;34(19):2372–5. doi:10.13699/j.cnki.1001-6821.2018.19.036.

8. Fonseca DA, Amaral I, Pinto AC, Cotrim MD. Orphan drugs: major development challenges at the clinical stage. *Drug Discovery Today* Mar. 2019;24(3):867–72. doi:10.1016/j.drudis.2019.01.005.
9. Kempf L, Goldsmith JC, Temple R. Challenges of developing and conducting clinical trials in rare disorders. *American Journal of Medical Genetics Part A* Apr. 2018;176(4):773–83. doi:10.1002/ajmg.a.38413.
10. Dechartres A, Riveros C, Harroch M, Faber T, Ravaud P. Characteristics and Public Availability of Results of Clinical Trials on Rare Diseases Registered at Clinicaltrials.gov. *Jama Internal Medicine* Apr. 2016;176(4):556–8. doi:10.1001/jamainternmed.2016.0137.
11. Rees CA, Pica N, Monuteaux MC, Bourgeois FT. Noncompletion and nonpublication of trials studying rare diseases: A cross-sectional analysis. *Plos Medicine* Nov. 2019;16(11):e1002966. doi:10.1371/journal.pmed.1002966.
12. Sakate R, Fukagawa A, Takagaki Y, Okura H, Matsuyama A. Trends of Clinical Trials for Drug Development in Rare Diseases. *Current clinical pharmacology*. 2018 2018;13(3):199–208. doi:10.2174/1574884713666180604081349.
13. He J, Tang M, Zhang X, et al. Incidence and prevalence of 121 rare diseases in China: Current status and challenges. *Intractable & rare diseases research*. 2019-May. 2019;8(2):89–97. doi:10.5582/irdr.2019.01066.
14. Shi XM, Liu H, Wang L, et al. Study on the current situation of China's First List of Rare Diseases based on 15 million hospitalizations. *Zhonghua yi xue za zhi*. 2018-Oct-30 2018;98(40):3274–3278. doi:10.3760/cma.j.issn.0376-2491.2018.40.012.
15. The State Council. State Council’s opinions on reforming the examination and approval system for drug and medical devices. Aug 18. 2015 (in Chinese). http://www.gov.cn/zhengce/content/2015-08/18/content_10101.htm (accessed June 3, 2021).
16. The General Office of the Central Committee of the Communist Party of China, the General Office of the State Council. The General Office of the Central Committee of the Communist Party of China and the General Office of the State Council issued the. “Opinions on deepening the reform of the examination and approval system and encouraging the innovation of pharmaceutical medical devices”. Oct 8, 2017 (in Chinese). http://www.gov.cn/zhengce/2017-10/08/content_5230105.htm (accessed June 3, 2021).
17. China Food and Drug Administration. Opinions of the General Administration on encouraging drug innovation to implement priority review and approval. Food and Drug Administration chemical tube (no. 126 of 2017). Dec 28, 2017 (in Chinese). http://www.nmpa.gov.cn/WS04/CL2196/324193.html (accessed June 3, 2021).
18. National Health Committee. Notice on printing and distributing the catalogue of the first batch of drugs to encourage imitation. (no. 744 of 2019). Oct 9,2019(in Chinese).http://www.nhc.gov.cn/yaozs/s7656/201910/38e3961482c04b59a2aa3e36106b1a4f.shtml (accessed June 3, 2021).

19. Bell SA, Smith CT. A comparison of interventional clinical trials in rare versus non-rare diseases: an analysis of ClinicalTrials.gov. *Orphanet Journal of Rare Diseases* Nov. 2014;26:9170. doi:10.1186/s13023-014-0170-0.
20. National Heath Committee. Notice on printing and distributing the requirements for the work of the construction of the major clinical drug evaluation technology platform for major new drugs. Jan 21. 2019 (in Chinese). http://www.nhc.gov.cn/qjjys/s3593k/201901/f4b2ff724a564b35964b296b427b9002.shtml (accessed June 3, 2021).

Figures

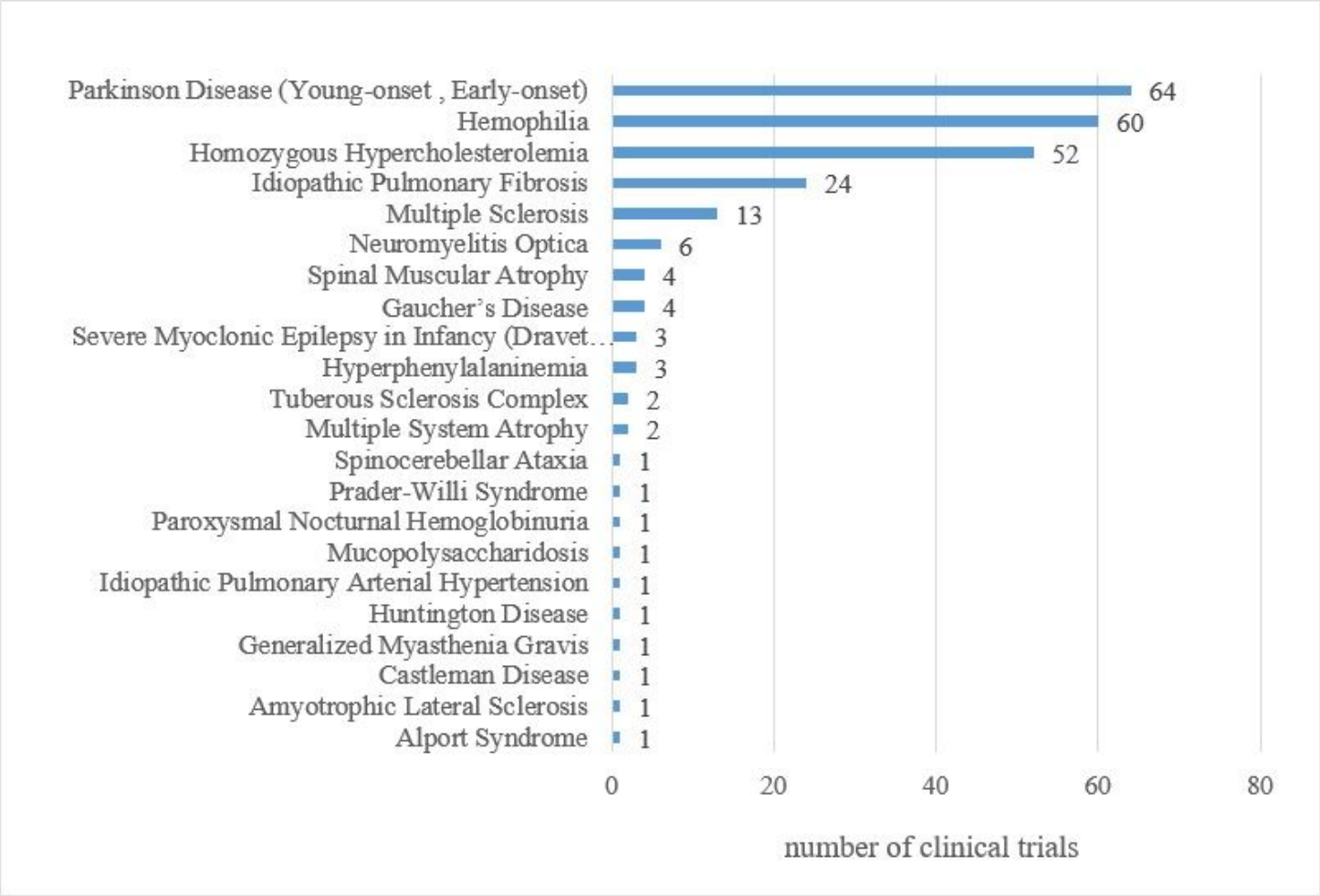


Figure 1

Number of clinical trials for different rare disease

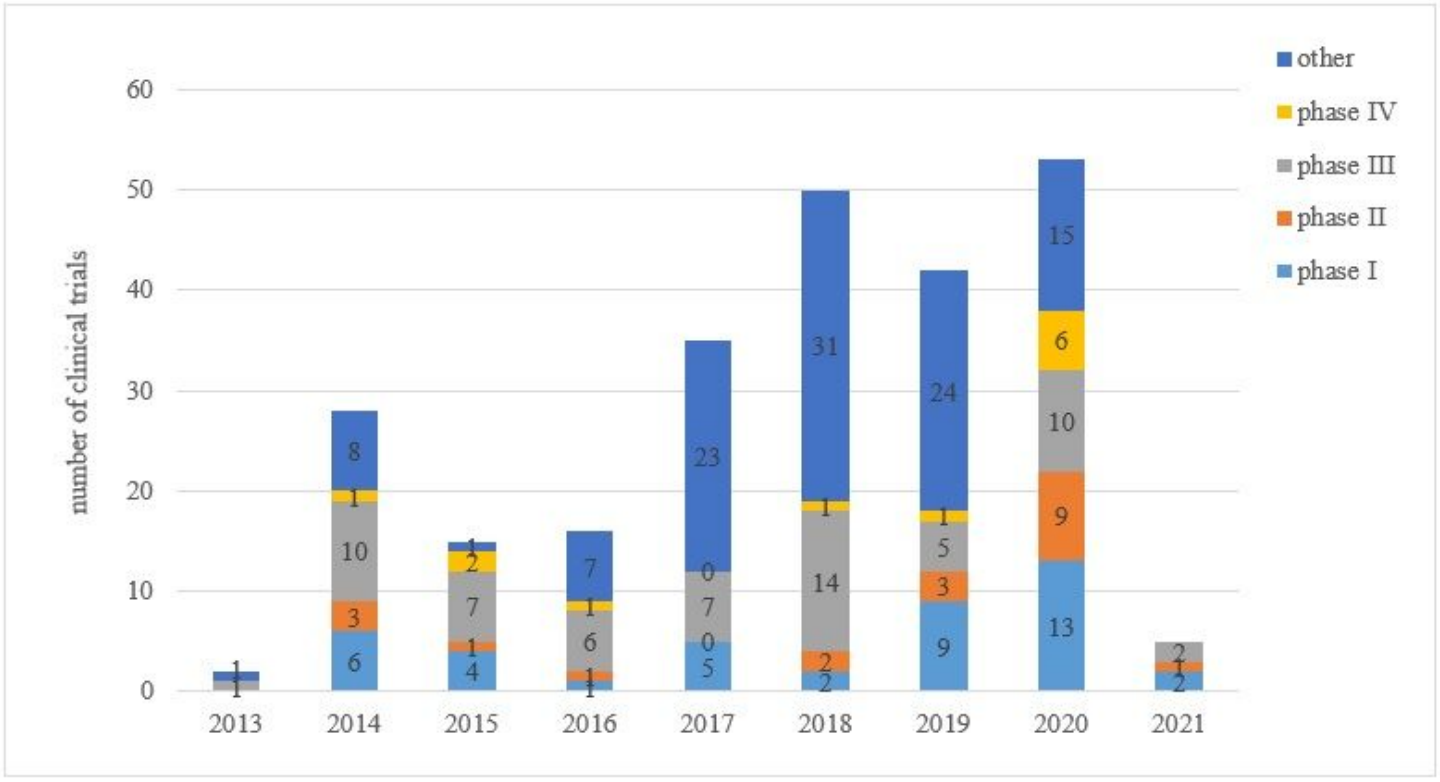


Figure 2

Annual numbers of clinical trials of orphan drugs by study phase

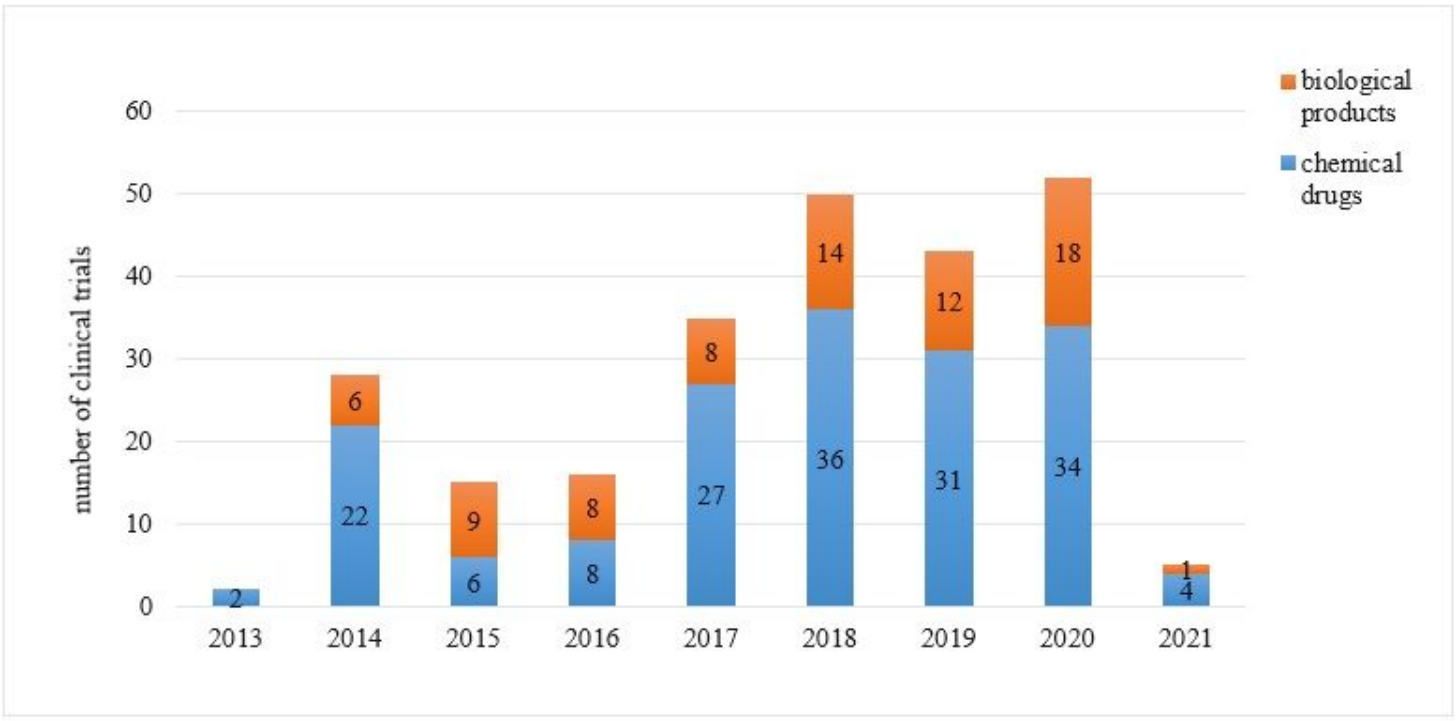
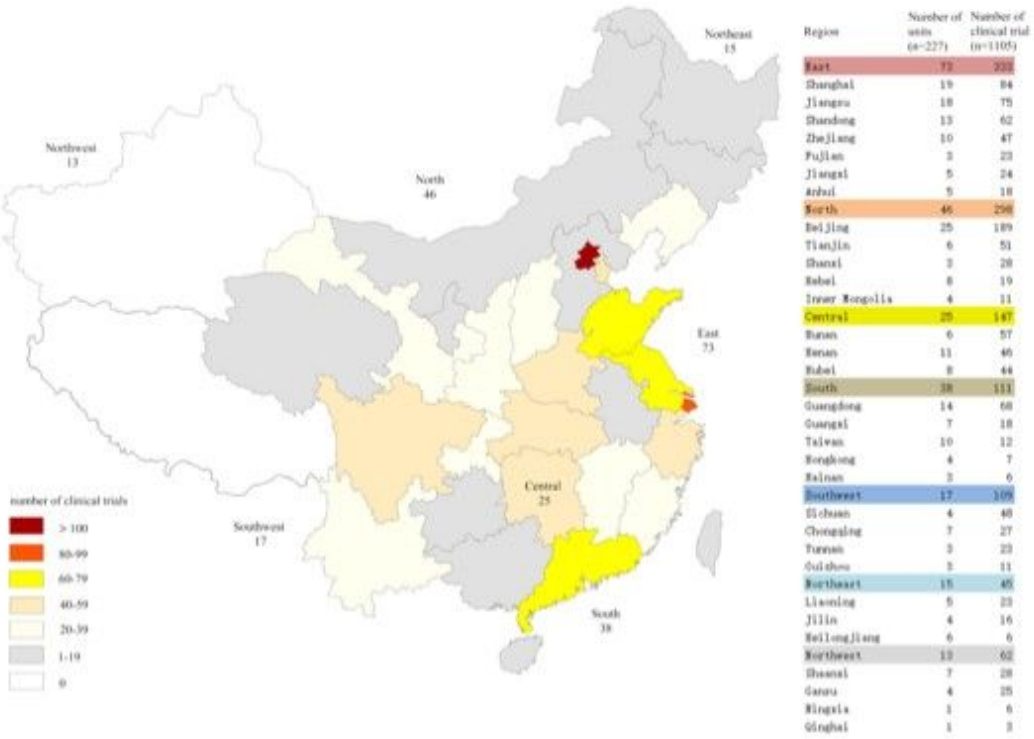


Figure 3

Annual numbers of clinical trials of orphan drugs by drug type

Figure 4

Annual numbers of clinical trials of rare disease by trial scope



Region	Number of units (n=227)	Number of clinical trial (n=1105)
East	73	332
Shanghai	19	84
Jiangsu	18	75
Shandong	13	62
Zhejiang	10	47
Fujian	3	23
Jiangxi	5	24
Anhui	5	18
North	46	298
Beijing	25	189
Tianjin	6	51
Shanxi	3	28
Hebei	8	19
Inner Mongolia	4	11
Central	25	147
Hunan	6	57
Henan	11	46
Hubei	8	44
South	38	133
Guangdong	14	68
Guangxi	7	18
Taiwan	10	12
Hongkong	4	7
Hainan	3	6
Southwest	17	109
Sichuan	4	40
Chongqing	7	27
Yunnan	3	23
Guizhou	3	11
Northeast	15	45
Liaoning	5	23
Jilin	4	16
Heilongjiang	6	6
Northwest	13	62
Shaanxi	7	28
Gansu	4	25
Ningxia	1	6
Qinghai	1	3

Figure 5

Geographical distribution of clinical trial units of clinical trials of rare disease