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R&D imbalance in rare-disease medicines in China: A cross-sectional analysis of clinical trial registrations and coverage by the national rare-disease catalogue

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R&D imbalance in rare-disease medicines in China: A cross-sectional analysis of clinical trial registrations and coverage by the national rare-disease catalogue

Abstract

Objective： From the perspective of R&D resource equity, this study systematically describes the registration landscape of clinical trials for rare-disease drugs in China, evaluates the clinical development coverage of diseases included in the two batches of China's Rare Disease Catalogue, and identifies major R&D gaps and structural problems.

Methods： We retrieved data from the National Medical Drug Clinical Trial Registration and Information Disclosure Platform up to 15 August 2026. Search terms comprised official standard names and common aliases of the 207 disorders listed in the two-batch Rare Disease Catalogue. Two independent trained investigators performed screening and verification. Drug-based interventional clinical trials were enrolled according to pre-defined criteria. Information including trial registration number, trial phase, drug category, sponsor, indication, and first public release date was extracted. Descriptive statistics, chi-square test and Fisher's exact test were applied for between-group comparisons.

Results： A total of 1 256 eligible trials were included, covering 107 (51.7%) catalogue-listed diseases. The annual number of trials rose from 6 in 2013 to 192 in 2025, with marked acceleration after 2018. Chemical drugs accounted for 54.5% and biological products for 44.8%; domestic enterprises sponsored 68.2% of all trials. The top 10 diseases by trial volume cumulatively contributed to 53.4% of total trials, among which haemophilia, idiopathic pulmonary fibrosis and melanoma ranked highest. Numerically, diseases in the second catalogue batch showed higher trial coverage (58.1%) than those in the first batch (47.1%), though the difference was not statistically significant ($\chi^2 = 2.45$, $df = 1$, $P = 0.12$). Domestic sponsors conducted significantly more early-phase trials than foreign sponsors, with a statistically significant difference in phase distribution between the two groups ($\chi^2 = 241.25$, $df = 1$, $P < 0.001$). One-hundred catalogue-listed diseases had no registered clinical trials at all; inherited metabolic and endocrine diseases together made up 42% of these uncovered conditions.

Conclusions： The volume of registered clinical trials for rare-disease drugs in China has increased substantially. Nevertheless, R&D resources are heavily concentrated on a small number of diseases, leaving numerous rare diseases with no R&D activity, which indicates prominent inter-disease R&D imbalance. Policy incentives should be further tilted toward unmet medical needs in under-explored areas. Our findings may provide references for rare-disease R&D governance in other low- and middle-income countries worldwide.

Key words： rare disease; clinical trial; drug research and development; rare disease catalogue; R&D equity

Introduction

Rare-disease drug research and development has long been plagued by inherent obstacles, including small patient populations, difficulties in subject recruitment, and uncertain economic returns. Globally, structural imbalance is a core challenge for rare-disease governance across countries: orphan-drug R&D resources tend to concentrate on a few popular disease categories

such as oncology and haematological disorders, while numerous ultra-rare diseases remain in persistent R&D gaps. Over the past decade, however, China has rolled out a series of important policy adjustments. In 2018, five authorities led by the National Health Commission of the People's Republic of China issued the First Batch of Rare Disease Catalogue, which formally identified 121 rare diseases at the national level for the first time[1, 2]. In 2023, the Second Batch of Rare Disease Catalogue was released, expanding the catalogue to 207 diseases in total[3]. Meanwhile, reforms in drug review and approval have been continuously advanced, and regulatory pathways including priority review, conditional approval and breakthrough therapy designation have gradually become accessible for rare-disease therapeutics[4, 5]. Access to high-cost rare-disease medicines via national medical insurance negotiations has also accelerated markedly, with the annual treatment cost of some agents reduced to less than 100 000 Chinese yuan[6, 7]. Whether these combined policy measures have actually boosted real-world R&D activity, and whether they have promoted even distribution of R&D resources across all catalogue-listed rare diseases — or instead further concentrated investment in a small set of high-profile disorders — requires quantitative evidence derived from full-catalogue analyses.

Existing domestic studies on rare-disease drug development mostly focus on single diseases or specific drug classes. A small number of comprehensive reviews rely largely on bibliometric or policy document analysis, lacking systematic scanning of registered clinical trials[8-10]. One critical question remains: following the expansion of the national rare-disease catalogue, have R&D resources diffused proportionally to all listed diseases, or are they still confined to several "star diseases"? If the latter holds true, patients suffering from many catalogue-included conditions may still face the predicament of "being listed in the catalogue but having neither approved drugs nor ongoing clinical trials". Prior literature has paid more attention to the overall growth of R&D output, yet insufficiently addressed equity and structural imbalance in resource allocation across disease entities. Moreover, few studies have systematically evaluated both batches of the national Rare Disease Catalogue. Using publicly available data from the National Medical Drug Clinical Trial Registration and Information Disclosure Platform, this cross-sectional study analysed drug-related interventional clinical trials covering all 207 diseases in the two-batch catalogue, aiming to uncover the actual distribution and structural gaps of rare-disease drug R&D in China.

2 Materials and Methods

2.1 Data Source and Search Strategy

Data were obtained from the National Medical Drug Clinical Trial Registration and Information Disclosure Platform (http://www.chinadrugtrials.org.cn). Search terms included official standard Chinese names, standard aliases and English abbreviations for all 207 disorders contained in the First Batch of Rare Disease Catalogue (Document No. Guoweiyi Fa〔2018〕No.10, covering 121 diseases) and the Second Batch of Rare Disease Catalogue (Document No. Guoweiyi Fa〔2023〕No.27, covering 86 diseases). Searches were performed against the "indication" field of the platform. The data retrieval cutoff date was August 15, 2026.

Two trained investigators independently conducted retrieval and preliminary screening. Original datasets were generated after deduplication by trial registration number. Discrepancies in screening outcomes were adjudicated through discussion with a third investigator to guarantee completeness and accuracy of retrieval.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria: drug-based interventional clinical trials whose indications or study

objectives explicitly targeted catalogue-listed rare diseases and their direct severe complications, with no restrictions on trial phase or trial status.

Exclusion criteria:①bioequivalence/bioavailability trials;②trials for which rare-disease catalogue disorders were not the primary indication;③non-drug interventions (e.g. diagnostic reagents and medical devices);④non-interventional/observational studies;⑤duplicate registrations.

2.3 Data Extraction and Coding

For each eligible record, we extracted trial registration number, trial phase, drug category, sponsor name, indication, trial status, and first public release date.

Standardised mapping of indications: Two investigators independently mapped indication texts of each trial to the standard disease names in the Rare Disease Catalogue. The disagreement rate for mapping was controlled within 5%. Final outputs were cross-checked by a third investigator to reduce information bias.

Indications were standardised and mapped to corresponding disease entities and catalogue batches. Drugs were categorised as chemical drugs, biological products, or traditional Chinese medicines / natural products. Biological products were further subdivided into monoclonal antibodies, coagulation factors, cell therapy, gene therapy, enzyme replacement therapy, fusion protein / receptor agents, and others.

Sponsors were classified by entity name as domestic enterprises, foreign-funded enterprises, research / medical institutions, or others. Trial phases were categorised as Phase I, Phase I/II, Phase II, Phase II/III, Phase III, Phase IV, or “other”. The “other” category contained 39 trials (3.1%): including 21 pharmacokinetic / clinical pharmacological studies, 7 extension / follow-up studies, 4 trials with unspecified phase information, 3 combined Phase I-III studies, 3 post-marketing studies, and 1 exploratory study.

2.4 Statistical Analysis

Descriptive statistics were applied to summarise baseline characteristics of included trials. Categorical variables were presented as frequency (percentage, %).

Core outcome indicators were defined as follows:Disease coverage rate: the proportion of catalogue-listed diseases with at least one registered drug interventional clinical trial among all 207 diseases in the two-batch Rare Disease Catalogue.R&D concentration ratio (CR10 / CR20): the proportion of total trials contributed by the top-10 and top-20 diseases ranked by trial count, respectively.

The chi-square test was used to compare disease coverage rates between the two catalogue batches, as well as phase distribution differences between domestic and foreign-funded sponsors. Fisher’s exact test was adopted for datasets with insufficient theoretical frequencies. The significance level α was set at 0.05. Data cleaning and statistical analyses were performed using R 4.6.0. This study used aggregated publicly available registration data without identifiable individual patient information; therefore, ethical approval was not required.

3 Results

3.1 Search and Screening Process

A total of 3 166 records were retrieved from database searching. After removing multi-term duplicates, 2 382 unique registrations remained. Following step-by-step screening, 1 048 bioequivalence / bioavailability trials, 28 trials with non-catalogue primary indications, 7 non-drug intervention studies, 26 non-interventional / observational studies, and 17 duplicate registrations

were excluded. Ultimately, 1 256 drug-based interventional clinical trials were included for analysis (Figure 1).

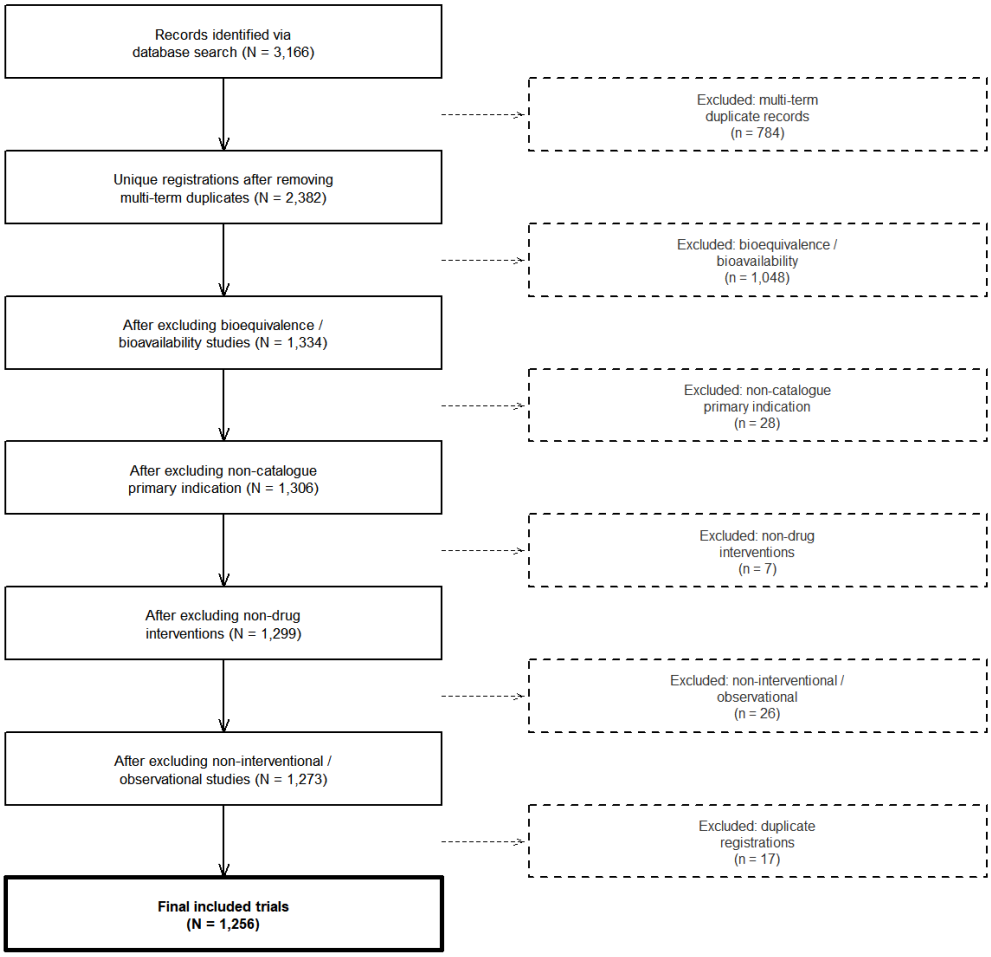


Figure 1：Flowchart of data screening

3.2 Overall Characteristics

Among the 1 256 included trials（Figure 2）, Phase I trials were the most frequent (437, 34.8%), followed by Phase III trials (374, 29.8%), Phase II trials (252, 20.1%), Phase I/II trials (77, 6.1%), Phase IV trials (56, 4.5%), Phase II/III trials (21, 1.7%), and 39 trials categorised as “other” (3.1%).

In terms of drug types, there were 685 chemical-drug trials (54.5%), 563 biological-product trials (44.8%), and merely 8 trials involving traditional Chinese medicines/natural products (0.6%). Within biological-product trials, monoclonal antibodies accounted for 137 trials (24.3%), coagulation factors for 105 trials (18.7%), cell therapy for 50 trials (8.9%), gene therapy for 26 trials (4.6%), and enzyme replacement therapy for 7 trials (1.2%).

Regarding sponsors, domestic enterprises sponsored the majority of trials (857, 68.2%), foreign-funded enterprises sponsored 365 trials (29.1%), and research/medical institutions sponsored 32 trials (2.5%). As for trial status, 649 trials were ongoing (51.7%), 511 were completed (40.7%), 80 were actively terminated (6.4%), and 16 were voluntarily suspended (1.3%).

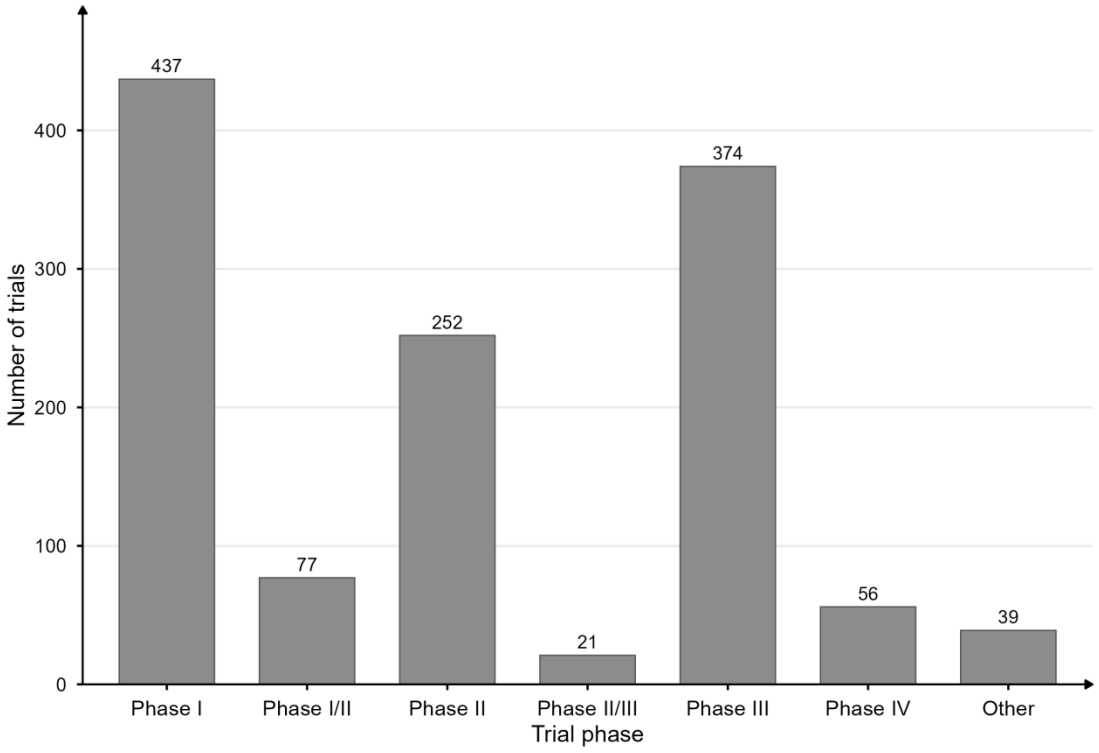


Figure 2：Distribution of rare disease drug clinical trial numbers across different trial phases in China

3.3 Temporal Trends

Distribution based on the first public release year demonstrated that the annual number of trials rose from 6 in 2013 to 44 in 2018, 87 in 2020, 138 in 2021, 151 in 2023, 189 in 2024, and 192 in 2025. A total of 137 trials were registered from 2013 to 2017, with an annual average of 27.4 trials; 962 trials were registered from 2018 to 2025, corresponding to an annual average of 120.3 trials. By the retrieval cutoff date in 2026, 157 trials had been publicly released. Given the incomplete calendar-year data for 2026, these 157 trials were excluded from annual-average calculation (Figure 3).

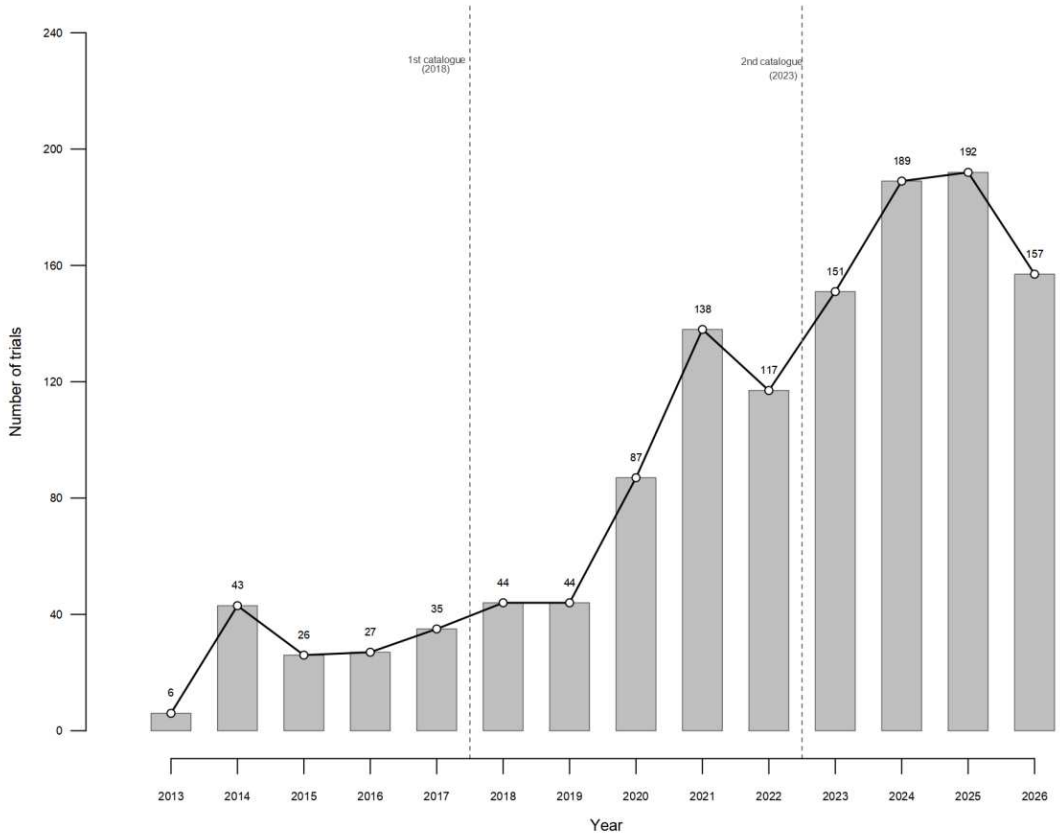


Figure 3：Temporal trends of annual registered rare disease drug clinical trials in China from 2013 to 2025

3.4 Disease Coverage and R&D Concentration

The included trials covered 107 out of 207 catalogue-listed diseases (51.7%). Fifty-seven out of the 121 diseases in the first-batch catalogue had registered trials (47.1%), versus 50 out of the 86 diseases in the second-batch catalogue (58.1%). Although trial coverage was numerically higher for diseases in the second batch, the difference was not statistically significant ($\chi^2 = 2.45$, df = 1, P = 0.12). The top 10 diseases ranked by trial volume accounted for 53.4% of all included trials (CR10 = 53.4%). The top-20 diseases are illustrated in Figure 4.

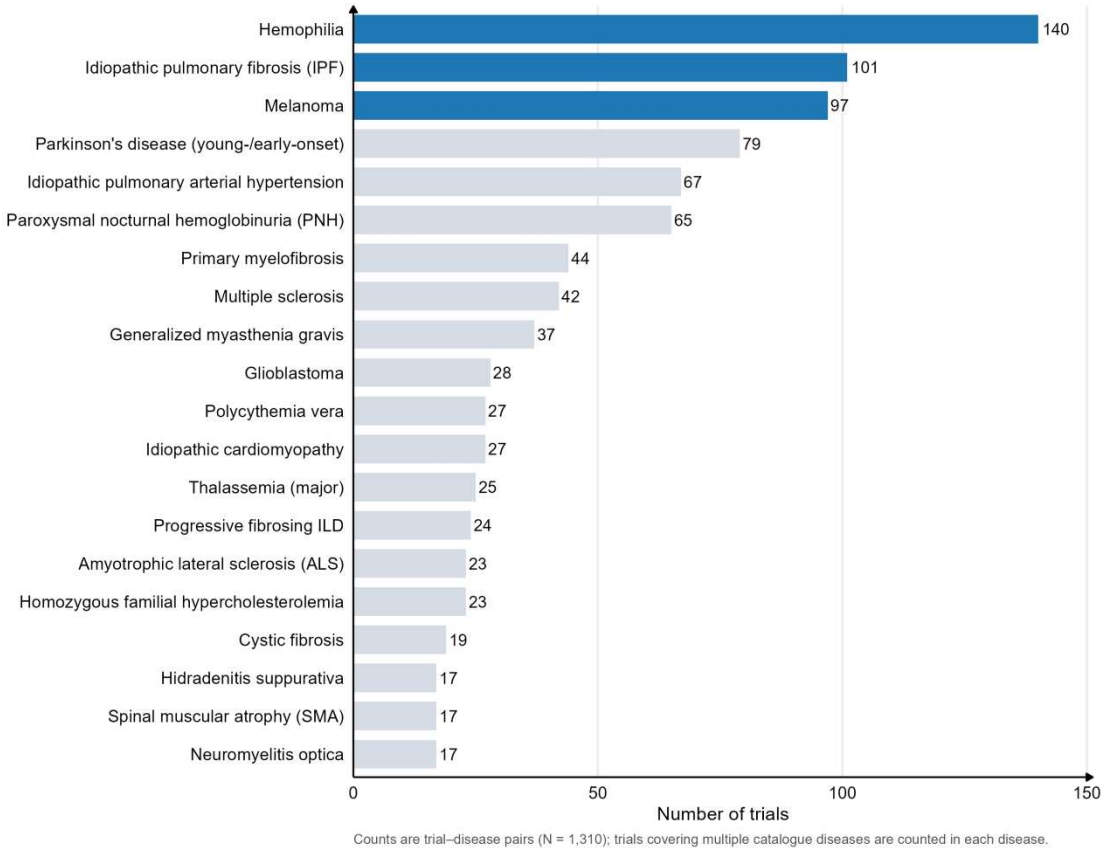


Figure 4：Distribution characteristics of the top 20 rare diseases by clinical trial volume

3.5 Stratified Analysis of Trial Phase by Drug Type and Sponsor

For chemical drugs, there were 271 Phase I, 149 Phase II and 187 Phase III trials. For biological products, there were 165 Phase I, 97 Phase II and 186 Phase III trials. Biological products had considerably more Phase I/II trials (57) than chemical drugs (20) (Table 1).

When stratified by sponsor type, domestic enterprises contributed 371 Phase I trials, far exceeding the 48 Phase I trials from foreign-funded enterprises. By contrast, foreign-funded enterprises conducted more Phase III (205) and Phase IV (43) trials than domestic enterprises (166 Phase III and 13 Phase IV trials, Table 2). To satisfy statistical assumptions, trial phases were grouped into early-phase trials (Phase I + Phase I/II) and late-phase trials (Phase III + Phase IV) for comparison between domestic and foreign-funded sponsors. The phase-distribution difference between the two sponsor groups was statistically significant ($\chi^2 = 241.25$, $df = 1$, $P < 0.001$).

Drug Type	Phase I	Phase I/II	Phase II	Phase II/III	Phase III	Phase IV	Other	Total
Chemical Drugs	271	20	149	10	187	29	19	685
Biological Products	165	57	97	11	186	27	20	563
Traditional Chinese Medicines/ Natural Products	1	0	6	0	1	0	0	8
Total	437	77	252	21	374	56	39	1256

Table 1：Cross-Tabulation Table: Drug Type × Trial Phase

Sponsor Type	Phase I	Phase I/II	Phase II	Phase II/III	Phase III	Phase IV	Other	Total
Domestic Enterprises	371	74	185	12	166	13	36	857
Foreign Enterprises	48	2	56	9	205	43	2	365
Research/Medical Institutions	17	1	10	0	3	0	1	32
Unknown	1	0	1	0	0	0	0	2
Total	437	77	252	21	374	56	39	1256

Table 2：Cross-Tabulation Table: Sponsor Type × Trial Phase

3.6 Diseases Without Registered Clinical Trials

Among the 207 catalogue-listed diseases, 100 diseases (48.3%) had zero registered drug-interventional clinical trials. Systemic classification showed that uncovered diseases were most frequently inherited metabolic disorders (28 diseases), followed by endocrine diseases (14 diseases); these two groups together constituted 42.0% of all uncovered diseases. Tumour-related rare diseases exhibited the lowest proportion of unmet R&D need, with a disease coverage rate of approximately 71.4%. Among otological disorders, non-syndromic deafness had no registered trials at all.

4 Discussion

This study revealed a substantial increase in the number of registered clinical trials for rare-disease drugs in China over the past decade, rising from single-digit annual outputs in 2013 to nearly 200 trials in 2025, with an inflection point of growth occurring around 2019. Given the release of China's First Batch of Rare Disease Catalogue in 2018 and the subsequent roll-out of supporting policies including priority review and medical insurance access, it is reasonable to link the growing R&D activity to these policy initiatives[5, 7]. Nevertheless, the structural characteristics underlying this growth merit greater attention: R&D resources have not diffused homogenously across rare diseases but are concentrated within a small subset of disease entities.

The top 10 diseases in terms of trial count accounted for more than half of all included trials; haemophilia, idiopathic pulmonary fibrosis and melanoma together contributed to over one-quarter of total trials. Such high R&D concentration is not unique to China. Globally, orphan-drug R&D tends to cluster around oncology and selected haematological conditions[11]. Four-decade data on US FDA orphan-drug designations indicate that roughly 20% of rare diseases attract more than 80% of global R&D pipelines, which echoes our finding of a CR10 value of 53.4%[12]. One key distinction, however, lies in disease priorities: inherited metabolic disorders and gene therapies represent popular orphan-drug R&D areas in Europe and North America. By contrast, nearly half of China's unaddressed R&D gaps correspond to inherited metabolic and endocrine diseases, suggesting that domestic rare-disease R&D is largely driven by rapid follow-up of well-validated targets, while translation capacity from basic frontier research to clinical practice remains limited. Haemophilia draws heavy investment from domestic firms owing to mature markets and well-established R&D pathways for replacement-based coagulation-factor therapies. Idiopathic pulmonary fibrosis benefits from clearly defined anti-fibrotic therapeutic targets. Melanoma, a neoplastic disorder listed in the Rare Disease Catalogue, receives abundant R&D attention mainly as part of broader anti-tumour drug

development efforts. Diseases pushed to the margins are ultra-rare conditions with extremely low incidence, poorly understood pathogenesis and few druggable targets, especially inherited metabolic and certain endocrine diseases[6, 13, 14]. Among the 100 catalogue-listed diseases with no registered trials, inherited metabolic disorders account for nearly 30%. Most of these conditions manifest in infancy or early childhood, feature complex sub-typing and have tiny single-disease patient pools, making them barely viable under conventional drug-development models.

Although the observed difference in disease coverage between the two catalogue batches failed to reach statistical significance, this finding carries important policy implications. Despite its later release date, the second-batch catalogue exhibited numerically higher trial coverage. This pattern arises from countervailing "time-effect" and "disease-structure-effect". The first-batch catalogue was published earlier and theoretically allowed a longer window for R&D accumulation. Meanwhile, the second batch incorporated more neoplastic and haematological diseases with pre-existing mature global R&D foundations, lowering the entry barriers for industrial follow-up research. The offsetting effects resulted in non-significant inter-batch differences. This observation suggests that current catalogue-related policies mainly stimulate research on diseases with pre-existing R&D foundations, whereas policy leverage remains insufficient for ultra-rare diseases with no prior research pipelines.

The phase-distribution discrepancy between domestic and foreign-funded sponsors also deserves careful interpretation. Domestic enterprises sponsored far more Phase I trials — almost eight-fold higher than foreign-funded sponsors — while foreign-funded sponsors dominated Phase III and Phase IV work, and this disparity was statistically significant. This pattern is subject to temporal confounding factors. A large proportion of early-phase trials by domestic enterprises were initiated after the 2018 policy reforms. In comparison, late-phase trials from foreign-funded sponsors mostly represent confirmatory studies of globally developed mature products conducted within China for local registration purposes. The two groups therefore differ substantially in their starting points and research timelines. On one hand, this demonstrates strong domestic industrial engagement in early-stage clinical research. On the other hand, it may reflect that many domestic Phase I studies represent generic development or fast follow-up of established targets rather than original innovative breakthroughs[7, 15]. Foreign-funded sponsors mostly bring already-marketed or late-stage candidate agents into China for local confirmatory trials to support registration. While this division of labour can improve drug accessibility in the short-term, insufficient progression of domestic-sponsored programmes into late-phase testing may compromise the long-term autonomy of China's rare-disease drug innovation ecosystem.

Current incentive policies predominantly accelerate marketing of existing candidate molecules but provide limited guidance for building de-novo product pipelines targeting R&D-gap diseases. Priority review pathways and national medical-insurance negotiations substantially reduce temporal and financial burdens for pharmaceutical developers, yet these policy tools only operate when candidate drugs are already available for review and negotiation[5, 6]. For the 100 catalogue-listed diseases without any registered clinical trials, such policies can hardly exert practical impact. To redirect R&D resources toward these neglected disease areas, upstream interventions are needed. First, establish national special programmes for natural-history studies and patient registries for rare diseases, filling gaps in epidemiological and natural-history evidence for uncovered conditions and lowering pre-investigation costs for industry. Second, deploy front-loaded incentive instruments such as extended market exclusivity periods and tax relief for

R&D expenditures specifically for ultra-rare diseases and conditions with zero existing pipelines, rather than relying solely on post-marketing regulatory acceleration measures. Third, accelerate the development of rare-disease-specific surrogate endpoints and expand the scope for real-world evidence in orphan-drug registration to reduce clinical-trial barriers for ultra-rare disorders. Fourth, promote Chinese participation in global multi-centre rare-disease clinical-trial networks to leverage international patient resources and accelerate research for gap diseases. These measures represent shared pathways for low- and middle-income countries to overcome bottlenecks in rare-disease drug development[13, 16]. Examples include dedicated national R&D funds, prolonged market-exclusivity terms, acceptance of real-world evidence for marketing authorisation, and funding for patient registries and natural-history research. Notably, many inherited metabolic disorders lack even reliable epidemiological data. Without such baseline information, enterprises cannot assess potential market size, resulting in low R&D willingness[6].

Several limitations of this study should be acknowledged. First, the registration platform only captures regulatory-required interventional clinical trials. Investigator-initiated exploratory studies, compassionate-use programmes and unregistered clinical observations were not included. Consequently, the true scale of rare-disease-related research activity may be underestimated. Second, although manual cross-checking was implemented for indication standardisation, ambiguous indication descriptions in some registry entries may have introduced misclassification bias. Third, data for 2026 remain incomplete; trend analyses are therefore primarily based on data spanning 2013-2025. Furthermore, this study only assesses the presence or absence of registered trials. It does not evaluate trial design quality, research success rates or the extent to which trials address unmet clinical patient needs, which warrant further multi-data investigations. Fourth, given the cross-sectional design of this work, we can only report correlation between policy implementation and rising trial numbers rather than establish causal inference. Fifth, our evaluation is restricted to whether trials exist. We did not examine trial quality, participant-recruitment challenges or R&D success rates and thus cannot fully reflect real-world clinical benefits for patients.

5 Conclusions

Driven by relevant policies, the number of registered clinical trials for rare-disease drugs in China has grown rapidly. Nevertheless, research and development activities are highly concentrated in a small subset of diseases. More than half of the catalogue-listed rare diseases have no registered clinical trials, highlighting prominent structural imbalance in R&D allocation across disease entities. A clear pattern has emerged whereby domestic enterprises dominate early-phase research, while foreign-funded enterprises take the lead in late-phase confirmatory trials.

While continuously optimising review-and-approval procedures and medical-insurance linkage mechanisms, future policies should prioritise addressing the structural issue of “catalogue-listed status accompanied by R&D gaps”. Upstream incentive measures need to guide R&D resources toward ultra-rare diseases such as inherited metabolic disorders. As the world’s largest developing country, China’s experience and dilemmas in rare-disease drug development offer valuable references for other low- and middle-income countries that have established their own rare-disease catalogues. Rare-disease policies should pursue not merely overall R&D growth, but also equity in research-resource distribution across different disease conditions.

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