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Dynamic clinical trial success rates for drugs in the 21st century

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Ying Zhou[1,8], Yintao Zhang[1,8], Hangwei Xu[1,8], Zhen Chen[1], Shijie Huang[1], Yinghong Li[1], Jianbo Fu[2], Hongning Zhang[1], Donghai Zhao[1], Xichen Lian[1], Yuan Zhou[1], Xinyi Shen[3], Kaixuan Liu[1], Yunqing Qiu[4], Yanzhong Wang[5], Wanqing Xie[6], Lianyi Han[7], Haibin Dai[1] & Feng Zhu[1]

In clinical drug development, two fundamental questions must be addressed: what is the success rate of drugs in clinical trial; how does such rate change over time. Here, a dynamic strategy for calculating *clinical trial success rate* (ClinSR) is proposed, which identifies that: the ClinSR has been declining since the early 21st century, yet it hits a plateau and recently starts to increase; the ClinSR for repurposed drugs is unexpectedly lower than that for all drugs in recent years; and an extremely low ClinSR is found for anti-COVID-19 drugs. In-depth analysis reports great variations among the ClinSRs of various diseases, developmental strategies, and drug modalities. A platform *ClinSR.org* (https://ClinSR.org/), is then developed to show how ClinSRs change over time. All in all, this work enables accurate, timely and continuous assessment of ClinSRs, for now and the future, to aid pharmaceutical and economic decision making.

Drug discovery is characterized by a high attrition rate, resulting in limited annual approvals[1]. In clinical drug developments, two fundamental questions must be addressed: *what is the success rate of drugs in clinical trials*?[2] and *how do such rates change over time*?[3] The answers to these questions play critical role in guiding scientific and economic decisions for pharmaceutical company, investor and regulatory agency[4]. Particularly, the resulting success rates are reported to be useful for optimizing pipeline decisions of pharmaceutical companies[5], enabling prudent resource allocations and adjusting capital investment strategy of investors[4], and evaluating the effectiveness of regulatory policies in promoting innovation and addressing unmet medical needs[6]. Many studies have been working on addressing these questions (provided in Supplementary Table S1), and calculation approaches, represented by *path-by-path*[7] and *phase transition*[2], have been developed for success rate evaluation. Particularly, the *path-by-path* method is capable of accurately reconstructing "drug development path" by imputing missing clinical trials[7], and the *phase transition* one can compute the 'likelihood of approval' by multiplying the probabilities observed in each clinical stage[2]. Based on these proposed approaches, studies were published for measuring the clinical trial success rates of pharmaceutical industry within certain time frame[8–11], whereas others focusing on the specific therapeutic area or disease indication[12–18].

However, there is huge variation, ranging from 7% to 20%, in reported *clinical trial success rate* (ClinSR) among the existing studies[8–18], the underlying reasons of which may include: (*a*) *the heterogeneity of analyzed data* -- the studies relied either on the data of commercial database[8], undisclosed company data[9], or domain-specific data for certain diseases[13]; (*b*) *the difference in computing protocol* -- the calculations were distinct in the size of assessed time-window[8,14], methodology for imputation of missing data[7,11,12], etc.; (*c*) *the shift of studied time frames* -- some study targeted the turn of the century[10], while other analyzed the recent time frame[15]. In other words, direct comparison among those previously-reported ClinSRs can provide

[1]College of Pharmaceutical Sciences, The Second Affiliated Hospital, Zhejiang University School of Medicine, State Key Laboratory of Advanced Drug Delivery and Release Systems, Zhejiang University, Hangzhou, China. [2]Institute of Translational Medicine, Department of Health Sciences and Technology, ETH Zurich, Zurich, Switzerland. [3]Yale School of Public Health, Yale University, New Haven, USA. [4]School of Medicine, Westlake University, Hangzhou, China. [5]School of Life Course and Population Sciences, King's College London, London, UK. [6]Department of Intelligent Medical Engineering, School of Biomedical Engineering, Anhui Medical University, Hefei, China. [7]Department of Dermatology, Huashan Hospital, Fudan University, Shanghai, China. [8]These authors contributed equally: Ying Zhou, Yintao Zhang, Hangwei Xu. e-mail: zhufeng@zju.edu.cn

limited insight into how investments and technologies affect the progression of drug development[2–4], and a unified standard for data collection and ClinSRs calculation is thus demanded. Furthermore, due to the lag of time and termination in data collection, it is challenging for previous studies to timely report the ClinSRs of their publication year, and it is also impossible to update the ClinSRs for the coming decade. Thus, great interest lies in developing new strategy facilitating timely and continuous data collection, as well as the automated assessment of the latest ClinSRs.

Herein, a systematic analysis on dynamic *clinical trial success rate* (ClinSR) of drugs in the 21st century was thus conducted. *First*, a rigorous and reproducible procedure for data collection and ClinSR evaluation was established, which worked out the shift over time (from 2001 to 2023) of ClinSRs using 20,398 clinical development programs (CDPs) involving 9682 molecule entities. To cope with issue of data heterogeneity, several public databases characterized by transparent, accessible and up-to-date (ClinicalTrials.gov, Drugs@FDA, etc.) were used for data collection here. *Second*, a *dynamic* strategy for calculating ClinSRs was proposed. Different from the previous *static* ones, this strategy enabled continuous evaluations of and effective comparisons among annual ClinSRs. *Third*, an evaluation of ClinSR was performed from diverse perspectives (such as various disease classes, distinct developmental strategies, and different drug modalities), which offered valuable insight into the current direction of pharmaceutical research. *Finally*, a multi-functional platform *ClinSR.org* was developed online (https://ClinSR.org/) to realize the dynamic illustration of how ClinSRs change over time, realize the automated update of ClinSR for coming decade, and allow the customized evaluation of ClinSR for any drug group of interest. In summary, this study could help to continuously support the pharmaceutical decision-making for now and the future.

Method

Collection of drug information and procedure for data standardization

Data collection in this study consisted of two sequential procedures: (*a*) the accumulation of drug data from exiting databases, and (*b*) the data standardization facilitating subsequent analysis.

Collection of drug data from established databases

Comparing with other existing databases, the ClinicalTrials.gov had long been considered as one of the most influential resources of clinical trial drug and clinical testing information, which had rapidly expanded since 2007 due to the official supports from U.S. FDA (*2007 FDA Amendments Act* required all clinical trials to be registered into ClinicalTrials.gov). In this study, to ensure the reliability of clinical information and maintain the high criteria of data inclusion among different years, ClinicalTrials.gov was adopted as the resource for collecting the data of clinical trial drugs. To assess the diversity of ClinicalTrials.gov data, the locations of all clinical trials were analyzed. Supplementary Fig. S1 demonstrated the distributions of clinical trial data among continents: *North America* (32.5%, USA, Canada, etc.), *Europe* (39.7%, United Kingdom, France, etc.), *Asia* (19.5%, China, Japan, Korea, etc.), and *Others* (8.3%, Australia, Brazil, etc.), which showed that those drug development efforts started outside the United States were also included here.

Moreover, the data of approved drugs were systematically collected from the official website of U.S. FDA. As provided in Table 1, the explicit number of new drugs approved each year collected to this study was given, resulting in 828 molecular entities and 142 biological products approved and regulated by *Center for Drug Evaluation and Research* (CDER) and *Center for Biologics Evaluation and Research* (CBER), respectively. Notably, one molecular entity after its initial approval by either CDER or CBER could be approved for another indication (successful drug repurposing). Taking the *alemtuzumab* as example, it was first approved in 2001 for the treatment of *B-cell chronic lymphocytic leukemia*, and later approved in 2014 for *multiple sclerosis*, both of which had been collected to measure ClinSRs in this analysis. The numbers of successful repurposing projects for all drugs and those approved prior to 2000 each year are also given in Table 1. Particularly, a total of 98 drugs (approved before 2000 for one disease and later approved for another after 2000) were included into this study, and a total of 207 drugs (approved before 2000 for one disease and later tested in the clinical trials for another after 2000) were also collected. Taking the *cladribine* as an example, it was first approved in 1993 for the treatment of *hairy cell leukemia* and later approved in 2019 for *multiple sclerosis*. Another example would be *topiramate*, which was initially approved for *generalized tonic-clonic seizures* in 1996, followed by a clinical evaluation in Phase 3 for treating *obesity* in 2000. Based on the information in Table 1, it was obvious that the drug repurposing was quite active in the past two decades. Another two reputable databases included in this study for drug information collection are *Therapeutic Target Database*[19] and *DrugBank*[20], which facilitated this work by confirming drug modality, key pharmaceutical properties, physicochemical characteristics, etc. This information was crucial for ensuring the customized analysis of ClinSR for a particular group of clinical trial drugs.

Table 1 | The explicit numbers of annually approved drugs analyzed in this study, collecting from the official online site of the U.S. FDA

Year of approval	FDA CDER		FDA CBER	Drug repurposing	
	NDA	BLA	BP	All Repo	Pre-2000
ALL	628	200	142	454	145
2023	38	17	16	23	2
2022	22	15	8	31	5
2021	36	14	10	35	4
2020	40	13	5	35	4
2019	38	10	5	28	4
2018	42	17	3	26	3
2017	34	12	9	27	3
2016	14	8	4	18	2
2015	32	13	12	9	3
2014	30	11	10	28	8
2013	25	2	7	20	7
2012	31	8	4	17	6
2011	24	6	4	8	2
2010	14	7	5	12	8
2009	19	6	8	13	7
2008	21	3	5	13	2
2007	17	2	4	19	5
2006	18	4	4	17	11
2005	15	5	5	15	11
2004	30	6	0	20	16
2003	21	6	4	12	11
2002	19	6	3	12	6
2001	24	4	3	10	9
2000	24	5	4	6	6

A total of 828 molecular entities, including 628 new drug applications (NDAs) & 200 biologics license applications (BLAs), approved by FDA *Center for Drug Evaluation and Research* (FDA CDER) were collected. Moreover, a total of 142 biological products (BPs) approved by the FDA *Center for Biologics Evaluation and Research* (FDA CBER) were accumulated. The numbers of successful repurposing projects (All Repo) and repositioning count of pre-2000 approved drugs (Pre-2000) were provided.

Data standardization for the drugs in clinical trial

Clinical trial drug data were collected from ClinicalTrials.gov (version of Jan, 2024). To make it usable for our success rates analyses, several data standardization steps were sequentially applied. *First*, a number of trials were excluded from this analysis, such as the ones with no clinical status provided (did not indicating the phase status), the ones with no clear trial time provided, the ones with no drug tested (dental implant, liver transplant, aerobic exercise, etc.), the ones not designed for the efficacy-related studies (drug-drug interaction studies, etc.), and the ones with vague drug name. Taking the exclusion of stem-cell/other biologic-based projects with vague drug names as an example, many trials were identified, like NCT03259217, NCT04863066 and NCT04125329 with a drug name of "*stem cell product*", "*CAR-T cells*" and "*human umbilical cord mesenchymal stem cells*", respectively. Since these names were too vague to make the determination of whether they progressed to the next stage of development, they were excluded from this study. Meanwhile, for the clinical trials providing concrete drug names, such as NCT04443907, NCT05166070 and NCT04125329 with a name of "*genome-edited hematopoietic stem and progenitor cell OTQ923*", "*MSLN-CAR-T cell RD133*" and "*embryonic stem cells-derived mesenchymal stem cell MR-MC-01*", respectively, they were all included in this study. Additionally, the impacts of excluded trials on the ClinSR were assessed. Overall, 2.3% of all clinical trials retrieved from ClinicalTrials.gov were identified as having unclear drug name. An exclusion of this subset of trials may lead to an overestimation of ClinSR, as some of these trials may form the independent CDPs, and would be considered as "failure" if included into this analysis. However, we cannot arbitrarily include this subset into our work, as it would lead to excessive ClinSR underestimation. In other words, the exclusion of the trials with unclear name is necessary, though it will inevitably lead to a certain degree of ClinSR overestimation (excluded trials only account for less than 2.5% of the total trials retrieved from ClinicalTrials.gov). The in-depth analyses of specific therapeutic areas revealed that infection, immune system disease, and oncology are three of the most affected areas by trials with unclear name, which primarily originated from two drug modalities: *vaccines* and *cell therapies*, which indicated that their ClinSRs may be somewhat overestimated.

Second, detailed information for each trial was systematically collected, which included trial ID, drug name, developmental status (such as Phase 1, Phase 2/3), disease indication, master protocol, noninferiority trial, date of trial start/study completion, recruitment status, etc. Taking the master protocols (basket and umbrella trials) and noninferiority trials as an example, both were carefully standardized in our analysis. In particular, a basket trial (containing *n* diseases/histologic features) was split to *n* drug-disease projects (e.g., the *baricitinib* was tested by basket trial NCT05189106 for treating *neurodegenerative Alzheimer's disease* and *amyotrophic lateral sclerosis*, which was thus split to two drug-disease projects); an umbrella trial (studying *m* drugs in diverse population groups for single indication) was split to *m* drug-disease projects (e.g., *trastuzumab*, *durvalumab*, and *panitumumab* were clinically tested in umbrella trial NCT05845450 for treating molecularly selected *resectable colorectal cancer*, which was thus split into three drug-disease projects); and for noninferiority trials, only the experimental molecular entity other than the "active comparator" was adopted to form drug-disease projects (e.g., *dapaconazole* was tested in a noninferiority trial NCT02606383 for treating *tinea pedis*, while *ketoconazole* was used as active comparators. Only the experimental molecular entity *dapaconazole* was thus used to form drug-disease project).

Third, the potential incompleteness in the synonyms data of ClinicalTrials.gov could hamper the accurate tracking of the same drug over time, particularly in cases involving sponsor acquisitions or change in drug research codes. To address this problem, a multistep strategy was implemented to ensure the accurate classification of the same drug. *Step*-1, we leveraged the built-in synonyms library of ClinicalTrials.gov to provide synonym mappings for interventions, which helped us to discover most of the trials under different names but referring to the same drug (according to our experience, the built-in synonyms library of ClinicalTrials.gov is powerful, which can accurately map the synonyms for the vast majority of the drugs). *Step*-2, to further enhance the completeness of drugs' synonyms, the data from several established databases (such as: *AdisInsight*, *DrugBank*, *DrugMAP*, *Pharmaprojects*, *PubChem* and *TTD*) were systematically collected, which helped to find a number of synonyms data unavailable in the built-in synonym library of ClinicalTrials.gov. For example, "*NEOD001*" is the developmental code name of "*birtamimab*" during its early phase development, but they were not matched by the built-in library of ClinicalTrials.gov. In our study, these two synonyms were identified in *AdisInsight*, *DrugBank*, *DrugMAP*, *TTD*, etc., which were then included into the synonym library of this study. In other words, in this study these two names were classified as the same drug. *Step*-3, an in-depth manual checking was conducted to discover those mismatched by these established databases (different names belonging to different drugs), which were then removed from the resulting synonym data for ensuring the data accuracy. All in all, the multistep strategy above could help to ensure that the trials involving the same drug were grouped together, regardless of their naming variation. Additionally, to deal with the data of non-new molecular entities (NME) products, the method applied in previous publications[21,22] was adopted in our analysis. Particularly, the formulations, dosages or biosimilars of a drug for certain disease were merged to the same drug. That is to say, those non-NMEs would not be regarded as new drugs. Taking the *ivermectin* clinically tested for COVID-19 as example, *ivermectin powder* (NCT04681053) and *ivermectin injectable solution* (NCT04472585) were merged into a drug of *ivermectin*. This meant that *ivermectin in powder form* was not be treated as a new drug here.

Fourth, a multistep process was further adopted in this analysis to enable disease standardization and classification. *Step*-1, the synonyms of disease indications were matched based on a built-in library of ClinicalTrials.gov. Taking the COVID-19 as an example, ClinicalTrials.gov offered an extensive list of synonyms (over 20), which included *SARS-CoV-2 infection*, *coronavirus disease 2019*, *2019 nCoV infection*, *2019 novel coronavirus disease*, and so on. Leveraging this synonym library, we achieved the preliminary standardization of disease name. *Step*-2, standardized names were then mapped to WHO *International Classification of Disease* (ICD-11). ICD-11 featured a hierarchical classification system (spanning *Chapter*, *Category*, and *Subcategory*) that served to standardize disease nomenclature. In this study, we discovered the *Category*-level ICD codes for all diseases after name standardization. Taking *giant cell glioblastoma* as an example, the API of ICD-11 can automatically assign a *Subcategory*-level code of 2A00.00 to this disease. From this, we derive corresponding *Category*-level code of 2A00, which ultimately categorized this disease under "*brain cancer*". *Step*-3, during the aforementioned steps, certain disease names may fail to be automatically matched. In such cases, their corresponding ICD codes were determined through manual validation. Additionally, the manual check was also performed to verify the reliability of the results identified in previous steps. All in all, our analysis employed a standardized procedure for disease standardization and classification with minimal reliance on manual checking. *Finally*, according to the approach used in previous analysis[2], Phase 1/2 trials were considered as Phase 2, and Phase 2/3 trials were regarded as Phase 3 in the ClinSR assessments of this study.

Development program identification for a drug of distinct disease

The CDP of a drug for the treatment of a disease was formed by merging all trials of this drug treating the same disease, and those trials of this drug treating other diseases were used to generated new CDPs. In cases where a drug, particularly the anti-neoplastic one, begins its

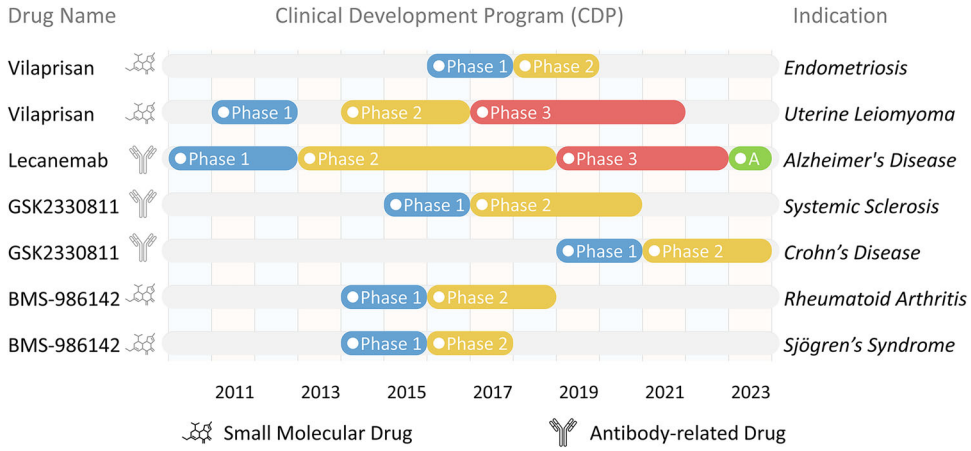

Fig. 1 | The definition of the *clinical development programs* (CDPs) based on drugs and their corresponding diseases. The CDP of a drug for the treatment of a disease was created by merging all trials of this drug treating same disease, and the trials of this drug treating other diseases were used to generate new CDPs. Taking *"vilaprisan"* as an example, it was clinically assessed for two diseases (*endometriosis* and *uterine leiomyoma*), which led to two distinct CDPs for this drug.

early-stage trials with a broadly-defined disease indication (e.g., *solid tumor*), but later continues its clinical development in a specifically-defined one (e.g., *lung cancer*), a method to aggregate CDPs was provided. Particularly, if the drug progresses to higher clinical phase (e.g., from Phase 1 to Phase 2) in a specific indication (such as *lung cancer*), the Phase 1 of *solid tumor* would be integrated with the Phase 2 trial of *lung cancer*; if the drug does not progress to a higher clinical phase and remains at an earlier stage (e.g., Phase 1), it would be retained with *solid tumor* to form a CDP of broad indication. This approach ensured that the development trajectory of the CDP was properly captured, particularly in cases where the drugs transitioned from broad disease indication in early-stage trial to a specific one in later phase. For specific CDP (treating the same indication), all trials were then filled into CDP based on their time of trial start & completion. If multiple trials of different statuses appeared in one year, only the one of highest phase would be considered. Taking the drug *vilaprisan* as an example (offered in Fig. 1), it had been tested in clinical trial for two indications (*endometriosis* and *uterine leiomyoma*), which led to two distinct CDPs for *"vilaprisan"*. All in all, a total of 20,398 CDPs corresponding to 9682 unique molecular entities for treating 910 disease indications defined by the WHO ICD-11 (*acute myeloid leukemia*, *cholera*, *hyperlipoproteinemia*, *migraine*, *thalassaemias*, etc.) were collected for analysis.

Strategy for calculating the clinical trial success rate (ClinSR) of studied drugs

Describing progression of clinical development program (CDP). To describe the progression of any studied CDP within a time-window, it is critical to know how drug's clinical status was changed. There were three clinical statuses (Phase 1, Phase 2 and Phase 3) that could be changed in a CDP. Taking the Phase 1 as an example, if it successfully progressed to a higher status (Phase 2, Phase 3 or approval) in a studied time-window, the progression under Phase 1 was considered to be *"Success"* in this work. There were some circumstances in which a clinical trial was considered as *"Failure"*: if a trial was labeled as *discontinued* or *terminated* in ClinicalTrials.gov and no new trial was initiated after this discontinuation/termination within the studied time-window; if a drug had not undergone new clinical trial for a disease for over 2-years (the rationale behind the selection of this *2-years* threshold for a period of time with no new trial were explicitly discussed in the following section entitled *"2.3.3 Determining the Threshold to Define Trial Failure"* and Supplementary Figs. S2-S3) and had not returned to active program in studied time-window. Otherwise, the progression under a trial was defined as *"Ongoing"*. It should be noted that if a trial progresses to higher phase (e.g., from Phase n to Phase $n+1$) within measured time-window, even if the time interval between the completion of Phase n and the initiation of Phase $n+1$ exceeds two-years, this trial would also be treated as *"Success"*. Taking *olokizumab* in the time frame of 2010–2018 as the example, although an interval between its completion of Phase 2 in 2013 (NCT01463059) and the initiation of Phase 3 in 2016 (NCT02760368) exceeded 2-years, Phase 2 was considered as "successfully progressed" to Phase 3 in 2010–2018. In other words, the CDPs brought back to active program would not be *"Failure"* here. Some drugs were approved from Phase 1 and Phase 2 (like accelerated approvals), which was especially the case for the rare disease space. Under this circumstance, a Phase 3 trial was usually missed from the CDP. To deal with this situation, the clinical progression from Phase 2 to Phase 3 was counted in this study, and so do the clinical progression from Phase 3 to approval. In other words, for a particular approval (e.g., accelerated approval), a direct jump from Phase 2 to approval will be regarded as the clinical progressions of both Phase 2 to Phase 3 and Phase 3 to approvals, which could effectively avoid possible "missing" of approvals. Meanwhile, if Phase 2 was missed, a strategy similar to the above one would be adopted, which will be considered as the clinical progressions of both Phase 1 to Phase 2 and Phase 2 to Phase 3.

Computing rates of overall success and phase success

To systematically assess the *clinical trial success rates* (ClinSRs) of drugs within a time-window (t_{begin}, t_{end}), four key measurements should be calculated, which included: $P1SR(t_{begin}, t_{end})$, $P2SR(t_{begin}, t_{end})$, $P3SR(t_{begin}, t_{end})$, and $OSR(t_{begin}, t_{end})$. Particularly, the *P1SR* denoted the success rate of clinical progressions from Phase 1 to Phase 2, the *P2SR* referred to the success rate of clinical progressions from Phase 2 to Phase 3, and the *P3SR* indicated the success rate of clinical progression from Phase 3 to final approval. Taking the $P1SR(t_{begin}, t_{end})$ as an example, the $n^1_{Success}(t_{begin}, t_{end})$ indicated the total numbers of *Success* Phase 1 progressions within the studied time-window, while the $n^1_{Failure}(t_{begin}, t_{end})$ denoted the total number of *Failure* Phase 1 progressions in the same time-window. Thus, the $P1SR(t_{begin}, t_{end})$ was used to calculate the success rate of the clinical

progressions from Phase 1 to Phase 2 using the following equation:

$$P1SR(t_{begin}, t_{end}) = \frac{n^1_{Success}(t_{begin}, t_{end})}{n^1_{Success}(t_{begin}, t_{end}) + n^1_{Failure}(t_{begin}, t_{end})} \quad (2.1)$$

Similarly, the success rates of clinical progressions from Phase 2 to Phase 3 and from Phase 3 to final approvals could be assessed by $P2SR(t_{begin}, t_{end})$ and $P3SR(t_{begin}, t_{end})$. Apart from the three key measurements for assessing *phase success rate*, $OSR(t_{begin}, t_{end})$ was adopted in this study to denote the *overall success rate (OSR)* from Phase 1 to approvals, which could be calculated by multiplying three *phase success rates P1SR*, *P2SR*, and *P3SR* using the following equation:

$$OSR(t_{begin}, t_{end}) = \prod_{i=1,2,3} PiSR(t_{begin}, t_{end}) \quad (2.2)$$

Determining the threshold to define trial failure

Based on our comprehensive literature review, a period of time with no new trial (PTnT) threshold of *"2-years"* was considered as *"failures"* by a variety of existing studies[22–24], which was, in our opinion, the summarization of authors' domain knowledge. In addition to *"2-years"*, a threshold of *"1-year"*[11] and *"1.5-years"*[8,25] were also reported by previous publications. Furthermore, several commercial databases (such as: *AdisInsight* and *IMS Health R&D Focus*) were reported to adopt 1.5-years or 2-years as indicators of "no development reported"[25,26], which implied that some of the available studies, such as[2] and[3], without clarifying their PTnT thresholds (but using commercial databases) might be based on the thresholds of *1.5-* or *2-years* in fact. All in all, our comprehensive literature reviews found that the selection of PTnT's threshold varied among existing studies, and none of them conducted the exploration of the rationale behind their selection of threshold. Although most of the analyses used *"1.5-years"* and *"2-years"* as thresholds, it remained challenging to conclude the optimal one for PTnT when determining the *"failure"* of clinical trials in a studied time-window.

Because of the possible subjectivity introduced by authors' domain knowledge, it was critical to perform objective (both *quantitative* and *statistical*) assessment on the robustness of our *"2-years"* assumption. Therefore, a method assessing such robustness by comparing with the *real* data was proposed. As described in Supplementary Fig. S2, N CDPs and their progressions within the *Studied Time-window* (light orange background) were illustrated. Theoretically, when calculating the ClinSRs for *Studied Time-window*, we did not know what would happen in *Later Time-period* (light blue background). However, since the *real* progression data in *Later Time-period* had been collected for all CDPs, we were able to rely on these *real* data to determine the *"failure"* of studied CDPs. For example, according to the *real* data of the *Later Time-period*, Phase 2 of CDP-1 should not be considered as *"Failure"* in the last year of *Studied Time-windows*; if a *1-year* threshold was used for PTnT, Phase 2 of CDP-1 would be regarded as *"Failure"*; if a *2-year* threshold was used, Phase 2 of CDP-1 would not be viewed as '*Failures*'. Under this circumstance, a *2-year* threshold could effectively reflect the *real* failure, while the *1-year* could not. Clearly, the CDP-3, CDP-6, CDP-7, CDP-9 & CDP-*N* were all *"Failures"* based on the *real* data. In other words, the *real* data could be used to evaluate whether threshold was appropriately set. The closer the OSRs (assessed based on a threshold) to the *real* OSRs, the more appropriately the threshold was selected.

For the *Later Time-period*, it was also important to provide each CDP an adequate period of time for determining the *"failures"*. In this study, a *Later Time-period* of five years was adopted, which was 2.5 times longer than the maximum threshold reported previously (*2-years*), and a sensitivity analysis on the selection of five years duration was demonstrated in Supplementary Fig. S3a. As offered on the left side of Supplementary Fig. S3a, all lines followed a similar trend with greatly limited variation among the OSRs of different durations. The robustness among durations were further given on the right side of Supplementary Fig. S3a. As shown, relative difference between the last two adjacent durations (5 to 6 years & 6 to 7 years) were consistently lower than 2%, which were significantly lower (p-values < 0.05) than that of the first two (3 to 4 years & 4 to 5 years). Moreover, no significant difference (*ns*) was found between the last two boxplots (5 to 6 years & 6 to 7 years) on the right side of Supplementary Fig. S3a, which denoted that a duration of ≥5 years was large enough for *Later Time-period*, and the minimum size of five years was therefore chosen to be the most appropriate duration in this study.

Based on the *real* data, we were finally capable of assessing the robustness of thresholds selection. As shown in Supplementary Fig. S3b, the orange line with triangle provided the OSRs based on *real* data, and the OSRs calculated based on different thresholds for PTnT were also described (three solid lines in green, black, and blue were based on the threshold of *1-year*, *2-years*, and *3-years*, respectively, and the threshold of the dash lines between two adjacent solid lines increased quarterly). As shown, the line of *real* OSR fell between the lines based on *2-years* and *1.75-years* thresholds. Supplementary Fig. S3c further demonstrated the relative difference between the line of the *real* OSRs and each of the lines using different thresholds. As provided, the lines based on *2-years* and *1.75-years* thresholds resulted in the lowest relative differences, when comparing with the line of *real* OSR (consistently lower than 10%), which might denote that these two were the most appropriate ones among all assessed thresholds. Although no significant difference was observed between the boxplots of *2-years* and *1.75-years* thresholds, we would like to select the *2-years* threshold to support the analyses in our study because of the following two reasons. *First*, the selection of *2-years* thresholds matched better with the annual-based nature of this study than *1.75-years*. *Second*, the lines using *real* data of the most recent time-windows in Supplementary Fig. S3b were much closer to the *2-years* line than the *1.75-years* one, which might give better description on the recent time-windows and the time-windows of the coming decades.

Finally, in-depth analysis on the intervals between the progression from one clinical phase to the next was systematically performed, and about 7.5% of the clinical trials were found taking longer than *2-years* to progress to the next phase. If 7.5% were included into our study by extending the thresholds (for example, from *2-year* to *3-year*), a large number of CDPs will not be regarded as *"Failure"*. For example, as descried in Supplementary Fig. S2, CDP-3, CDP-6, CDP-7, CDP-9, and CDP-*N* would be regarded as *"Failure"* if a *2-years* threshold was chosen, while only CDP-*N* was regarded *"Failures"* if shifting to a *3-years* threshold. The exclusion of four *"Failure"* CDPs would inevitably overestimate the OSR, which was the reason why the *3-years*-based OSRs were obviously higher than those of the *2-years*-based ones (illustrated in Supplementary Fig. S3b; overestimated by 5.2% in 2001–2009 time-window and 1.3% in 2010–2018 time-window).

Determining time-window size for calculating ClinSRs

Before assessing the success rate of clinical trial drugs, it was a prerequisite to set a time-window of *N* years size. To explore the variations induced by the selection of different window sizes, the sensitivity analyses were therefore performed in this study to determine the optimal size *N*, which were explicitly offered in Supplementary Fig. S4. Supplementary Fig. S4a provided the OSRs assessed based on seven different window sizes (from 6 years to 12 years); Supplementary Fig. S4b illustrated the relative differences between two colored lines in Supplementary Fig. S4a of the adjacent time-window size (for example, 8 to 9 years, 9 to 10 years, 10 to 11 years, etc.); and Supplementary Fig. S4c demonstrated the OSR calculated based on four window sizes (3 years, 4 years, 5 years, and 9 years). As offered in Supplementary Fig. S4a, all lines showed similar descending trend, and

the lines of 9 to 12 years shared much closer shape than that of 6 to 8 years. Such results indicated that the larger the time-window size, the more robust the dynamic OSRs. The robustness of the four lines (9 to 12 years) could be further identified in Supplementary Fig. S4b. As illustrated, the relative differences between the last three adjacent time-window sizes (9 to 10 years, 10 to 11 years & 11 to 12 years) were consistently lower than 5%, which were significantly smaller (p-values < 0.05) than that of the first three (6 to 7 years, 7 to 8 years, 8 to 9 years; 44.4% and 13.3% of their relative differences were larger than 5% and 10%, respectively). Meanwhile, no significant difference (*ns*) was found among the last three boxplots (9 to 10, 10 to 11 & 11 to 12 years) in Supplementary Fig. S4b, which indicated that the window size of ≥9 years was large enough to calculate ClinSRs, and the minimum size of nine years ($N = 9$) was therefore chosen. Moreover, Supplementary Fig. S4c provided a comparison among four different lines (3, 4, 5 and 9 years). It was apparent that much greater fluctuations were observed for the lines of 3–5 years, when compared with that of 9 years. Above results aligned well with the statements in previous study[27] that an appropriate window size should be large enough to offer a drug adequate period of time to reach its final fate, and an extended window was able to "draw reliable conclusions" for success rate assessment[5]. Taking together, our sensitivity analyses suggested that the selection ($N = 9$) here was appropriate in term of the robustness of the calculated ClinSRs. However, with the increase of the time-window size (from nine to twelve), there remained subtle differences among the calculated success rates. This highlighted that it was critical to maintain a consistent window size when comparing the ClinSRs, especially for the case requiring high resolution in success rate assessment. In other words, when it comes to a situation that the time-window size matters, the selection of nine-year time-window may not be appropriate enough, and our reported ClinSRs should be considered with caution.

All in all, a *dynamic* strategy for the measurement of ClinSR was proposed in this analysis, which integrated three key components: (*a*) publicly-available database, (*b*) effective data standardization, and (*c*) systematic assessment of strategy's robustness. Different from those previous "*static*" ones, our strategy enabled the continuous measurements of and effective comparisons among annual ClinSRs. The reason behind such abilities was largely due to the collection of data from publicly-accessible database (including ClinicalTrials.gov, Drugs@FDA, etc.), which were characterized by transparent, accessible and up-to-date. This data adoption approach was distinct from that of previous analyses relying on their own company data[9], the data of certain diseases[13], and the data of commercial database[2]. As known, the resulting ClinSRs of those available studies were highly data-dependent, which led to substantial difficulty in comparing the ClinSRs among time-windows. All in all, due to the integrations of three key components into this analysis, the assessment of the ClinSR variation among different time-windows was finally realized.

Ethical statement

As this study only used de-identified data from databases and did not have any access to potential identifiable information, this study is considered non-human subject research and therefore exempted by IRB and consent.

Results

Measuring the change of ClinSRs over time-windows for all drugs

With the dramatic investment increase and continuous technological advance during the past two decades[28], researchers were curious about how clinical trial success rate (ClinSR) was affected over time. Herein, the dynamics ClinSRs of 15 time-windows from the beginning of 21st century to now were assessed using CDPs and molecular entities (MEs). These two helped to answer the question: "what are the probabilities that a drug developed for a specific indication (CDPs-based) or any indication (MEs-based) will reach approval?"[2].

Dynamic ClinSRs evaluated based on clinical development programs (CDPs)

Figure 2a gave the change of CDPs-based ClinSRs over time. As shown, the *phase success rates* (PSRs) of P1SR, P2SR, and P3SR were described using bars in blue, yellow, and red, respectively, and the dark line with dots indicated the changes of OSR over time. It was clear that the OSRs had been declining over time, and remained stable around 5% in recent years. In other words, despite the extensive efforts made to almost every step of drug development[29], it remains in a dilemma. Herein, literature review was thus performed to find out potential causes driving the decline of OSRs. *First*, such decline was reported to be a "*natural consequence*"[30], because the low-hanging fruits being all harvested, leaving behind more difficult targets and drug candidates to work on. *Second*, the ever-expanding collection of approved drugs might introduce great complexity of new drug development process and raise the regulatory standard for approval[31]. *Third*, the surge in capital investment and clinical trial activities might further intensify the competition in drug development, making it very difficult for non-*first-in-class*/non-*best-in-class* drugs to achieve return on investment and ultimately leading to discontinuation[32]. Despite the potential causes, the falling success rates might also reflect more appetite and room for increased scientific risk in drug discovery, with the expectation for efficacy and safety continue to rise[33]. One reason behind the high OSRs at the early 21st century might partially come from the lack of mandatory trial registration policy. Particularly, the ClinicalTrials.gov data became increasingly comprehensive, due to the issuances of *International Committee of Medical Journal Editor* (ICMJE) policy[34] and *FDA Amendments Act* (FDAAA)[35] in 2004 and 2007, which indicated that some trials might be missing in ClinicalTrials.gov at the early time-windows, therefore likely inflating the OSRs at the early 21st century.

An in-depth analysis of Fig. 2a identified that the P2SRs (yellow) of every time-window were consistently lower than P1SR (blue) and P3SR (red), which indicated that Phase 2 (studying drug efficacy, assessing tolerability, finding appropriate dosages, evaluating safety, etc.) remained one of the most challenging steps in clinical drug development[36]. Similar result was identified by a variety of available studies[2,3,7,22]. Based on our literature reviews, some of the explanations might include: Phase 2 was assessed with the most critical eye before embarking on an expensive, resource-consuming, and risky Phase 3 trial[37], and some companies might become risk-averse to launching Phase 3 trials due to their limited tolerance for potential clinical trial risks. Moreover, P1SR (blue) was found to continuously decline from ~70% to ~50%, during the past two decades. As reported, the objectives of current Phase 1 evaluation were gradually expanded to assess some part of pharmacokinetics/pharmacodynamics and efficacy besides the previous safety evaluation[38], and the so-called "quick-kill" strategy rapidly adopted in pharmaceutical companies brought up more drug candidates to terminate the inferior ones in an earlier stage, especially Phase 1[39]. All these important factors might collectively contribute to the continuous declines of P1SR, but we had no way to know based on the current analysis. In the meantime, a recent analysis reported that the P1SR for clinical development of drugs in China across all diseases was only 34% (2011–2015) and 20% (2016–2020), which was much lower than the observation in this study (P1SR = ~50% in recent time-window of Fig. 2a). As reported, such discrepancy might result from the extensive variation among the regional regulatory frameworks of different countries[40].

It was also found in Fig. 2a that P3SR (red) had gradually declined since the beginning of this century, and in contrast to both P1SR and

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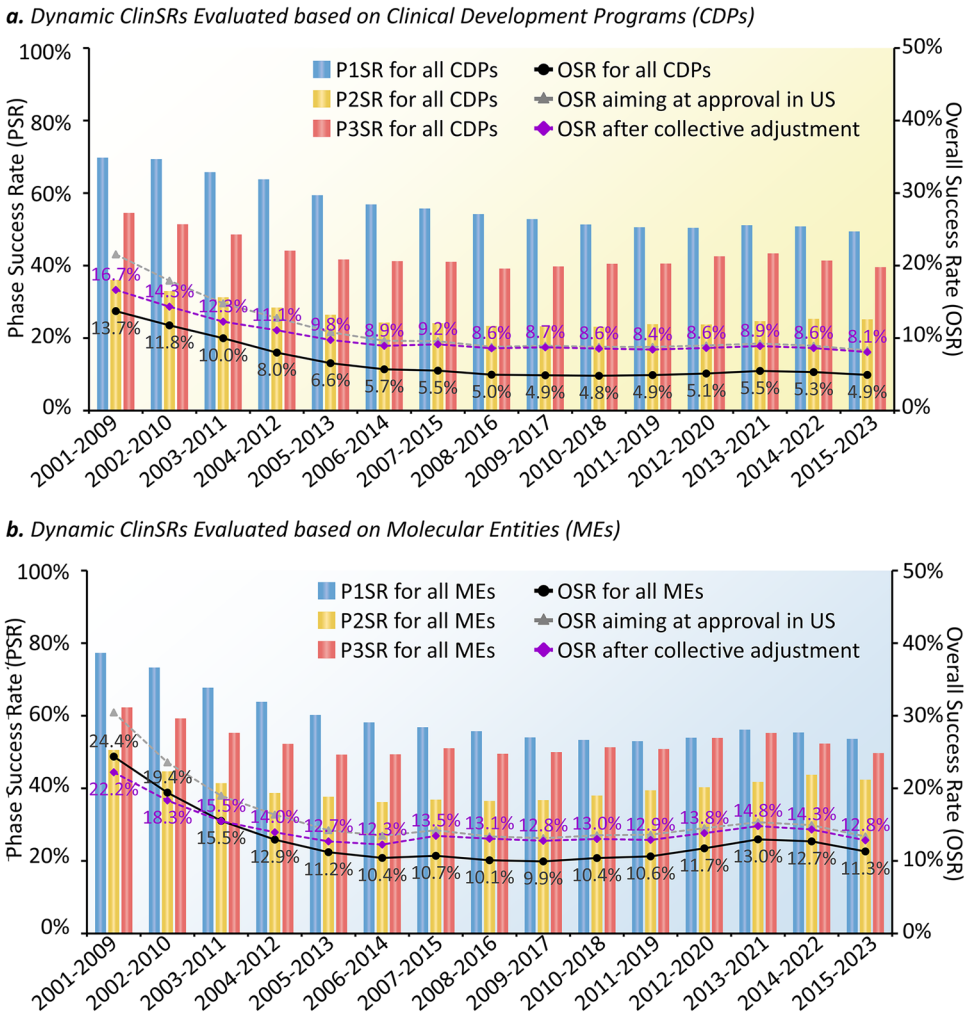

Fig. 2 | The dynamic *clinical trial success rates* (ClinSRs) calculated in this study. **a** Dynamic ClinSR assessed based on clinical development programs (CDPs). **b** Dynamic ClinSR evaluated based on molecular entities (MEs). A nine-year time-window was adopted to evaluate the ClinSR, providing a drug adequate period of time to reach its final fate and a total of fifteen time-windows (from 2001–2009 to 2015–2023, inclusive) were measured. The variations of *overall success rate* (OSR) for all CDPs/MEs over time were given using the *dark solid-line with dot*, while the OSRs for CDPs/MEs aiming at US approval discussed in the *Section 3.5.1* (*grey dash-line with triangle*) and for those after the *collective adjustment* proposed in the *Section 3.5.3* (*purple dash-line with diamond*) were described. The *phase success rates* (PSRs, including P1SR, P2SR and P3SR) for all CDPs/MEs were illustrated using bars in BLUE, YELLOW and RED, respectively. Source data are provided as a Source Data file.

P2SR, the P3SR demonstrated further decline in recent time-windows (from 2013–2021 to 2015–2023). It was reported that comparing with the protocol design of Phase 3 in 2001–2005, the complexity of that in 2011–2015, had increased by 70%[41]. Increased complexity also resulted in longer cycle time, higher numbers of protocol amendments, or lower patient recruitment/retention rate[41], which greatly contributed to the clear decline of P3SR in the first eight time-windows of Fig. 2a. Moreover, the further decline of P3SR in the recent three windows of Fig. 2a primarily came from the dramatic decreases of P3SR in some major disease classes, such as *infectious/parasitic disease*, *metabolic disease*, *circulatory system disease*, and so on. Taking the *infectious/parasitic diseases* as example, tremendous clinical trials for COVID-19 were tested, and the majority of the Phase 3 clinical trials were reported to end in failure[42], which contributed to the decline of P3SR in recent years. The impact of COVID-19 related clinical trials on ClinSR were further discussed in the following section.

Dynamic ClinSRs evaluated based on molecular entities (MEs)

Figure 2b showed the change of MEs-based ClinSRs over time, which identified a trend of OSRs (dark line with dots) similar to that of CDPs-based evaluation (as shown in Fig. 2a). Moreover, similar to Fig. 2a, the P2SR (yellow) of each time-window was found consistently lower than P1SR (blue) & P3SR (red), and the decline of both P1SR (blue) and P3SR (red) was observed in the past two decades. As a result, both CDPs-based and MEs-based evaluations revealed that the OSRs had been declining over times. However, the resulting MEs-based OSRs were consistently higher (almost two times) than that of the CDP ones (Supplementary Fig. S5a), and the MEs-based PSRs were identified to be higher than that of the CDP ones (Supplementary Fig. S5b). In other words, the CDPs-based calculation (considering all indications) tended to result in lower probability of success than the MEs-based one (regardless of different diseases). Reasons behind the difference between CDPs-based and MEs-based success rate assessments could be explained using the following scenario. A drug is developed for two diseases, and both progress from Phase 1 to 3, but one fails in Phase 3 and the other succeeds in gaining FDA approval. If based on MEs, success rate will be 100%, while CDPs-based assessment will give a 50% success for all diseases, which thus lead to a lower probability of CDPs-based success than the MEs-based one. Moreover, a marginal but noticeable increase in OSR were observed in 2012–2020 and the subsequent time-windows—rising from 12.9% for 2011–2019 to about 14.5% for the following time-windows as described in Fig. 2b, which was in

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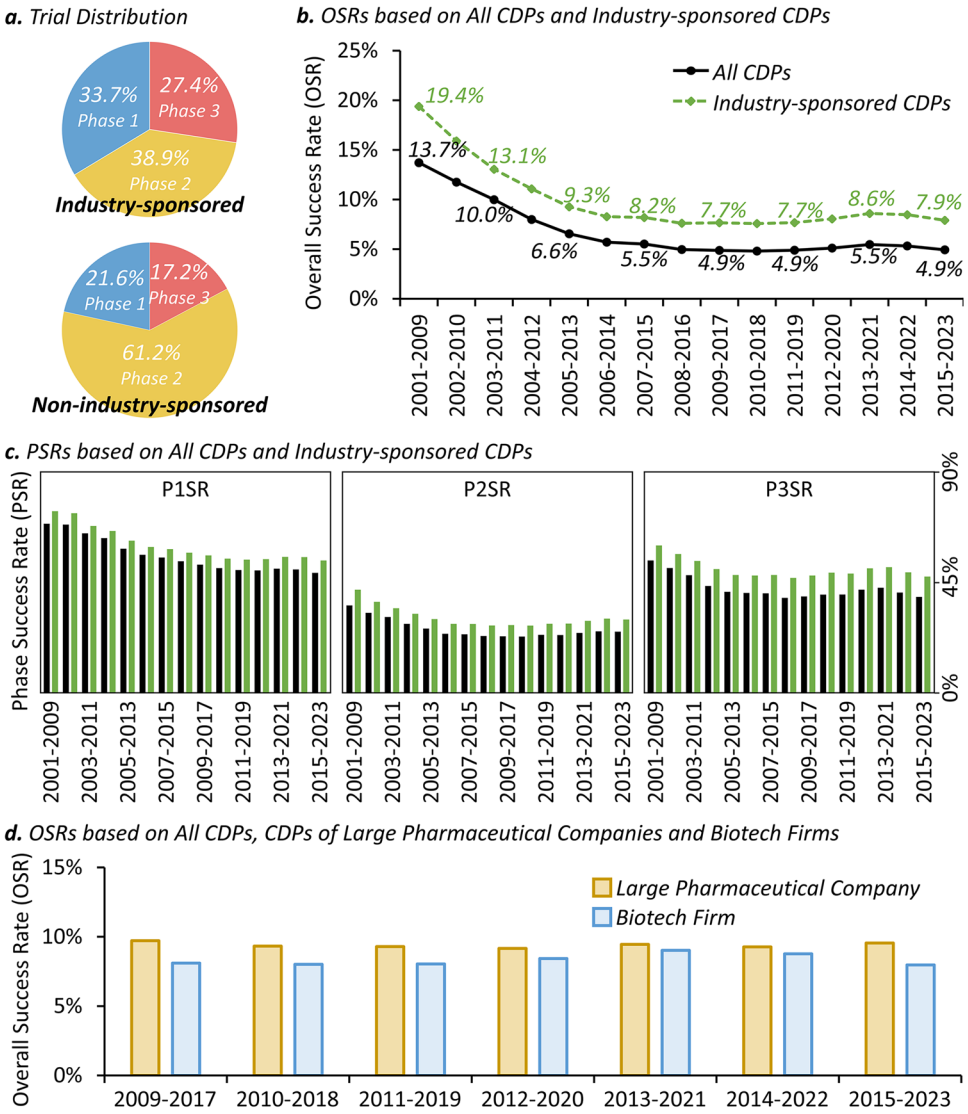

Fig. 3 | The dynamic *clinical trial success rates* (ClinSRs) using the industry-sponsored CDPs calculated in this study. a Distribution of industry- sponsored and non-industry-sponsored trials among different clinical status (Phase 1, 2, and 3). **b** The *overall success rates* (OSRs) based on industry-sponsored (dash line in green) and all (black line with dots) CDPs. **c** The *phase success rates* (PSRs) evaluated based on the industry-sponsored (green bar) and all (black bar) CDPs. **d** The OSRs for the CDPs of large pharmaceutical company (yellow bars) and those of biotech firm (blue bars). Source data are provided as a Source Data file. CDPs clinical development programs, P*n*SR phase *n* success rate.

accordance with those recent publications[28,43] reporting the gradual increase of trial success rate in recent years.

Dynamic ClinSRs evaluated based on industry-sponsored CDPs

The extra analyses differentiating the industry-sponsored CDPs from the non-industry-sponsored ones (for example, academic trials) were also conducted in this analysis. The *funder type* of trials in ClinicalTrials.gov was carefully identified, which grouped all trials in our study into: industry-sponsored, NIH-sponsored, and others (university/college-sponsored, hospital-sponsored, and so on). Figure 3a gave the distribution of trials among clinical statuses. The percentage of industry-sponsored Phase 3 trial (27.4%) was much higher than non-industry one (17.2%), which denoted that some academic trials (for example Phase 1 and 2) were mechanistic in nature, and there was no pre-specified intentions to progress to Phase 3[44]. Figure 3b, c provided *overall success rates* (OSR) and PSR of industry-sponsored (Green) and all (Black) CDPs, and both types of success rate for industry-sponsored trial were found higher than that of all trials. In other words, the above findings denoted that, for non-industry-sponsored trials (such as lack commercial backing), there was lower intention of pursuing regulatory approval[45].

Moreover, ClinSRs of large pharmaceutical companies and biotech firms were assessed, and the differences were further discussed. *First*, the data of *sponsor* in ClinicalTrials.gov were collected for each trial, and all those retrieved *sponsors* were manually checked to determine whether they were biotech firms or not. *Then*, the world's top-20 large pharmaceutical companies released by *Citeline* (https://insights.citeline.com/) were collected, and all the *sponsors* retrieved above were further checked to discover the trials initiated by top-20 companies. *Finally*, the ClinSRs for top-20 pharma companies and biotech firms in recent time-windows were computed. As provided in Fig. 3d, the OSRs for leading pharma company and biotech firm remained steady across time-windows, and the top-20 large pharma companies gave consistently higher OSRs (between 9.2% and 9.8%) than that of biotech firms (between 8.0% and 9.0%). Such result aligned roughly with recent publication[5] reporting the OSRs of 10.8% and 7.9%

for leading pharma companies and biotech firms. As reported, the potential factors contributing to the lower OSRs of biotechnology firms included the fewer development resources/capabilities and higher risk appetite inherent in their business models when comparing with those large pharmaceutical companies[5].

Diverse and dynamic ClinSRs measured based on disease classes

In addition to the ClinSR for all CDPs, it was of interests to further evaluate the ClinSR for CDPs of specific disease class. As shown in Supplementary Table S2, the OSRs of 14 disease classes (defined by WHO ICD-11) across fifteen time-window were systematically offered. Taking the latest time-window 2015–2023 as an example, there was substantial variation in the OSRs (from 2.6% to 18.5%) of different classes of diseases, which reminded us to perform further assessment on disease-specific ClinSRs. Thus, a review of the data that were collected to this study was conducted, which found three disease classes that covered the highest numbers of CDPs: *oncologic diseases*, *neurological diseases* and *infectious/parasitic diseases*. These classes had long been considered to be three of the most popular research domains in both academia and industry[46,47], which required an in-depth analysis in the following sections.

Assessing the ClinSRs for drugs treating oncologic disease

The dynamic ClinSRs evaluated based on the CDPs of *oncologic diseases* collected for this study were explicitly described in Supplementary Fig. S6. As shown, the OSRs had been declining over time; since the time-window of 2006–2014, the OSRs kept below 5% with small fluctuations among recent time-windows. As reported, those potential contributors to such low rate of success might include limited understanding of cancer biology, poorly predictive preclinical models, and heterogeneity among patients[48,49]. On the one hand, P2SR was found consistently lower than P1SR and P3SR in recent time-windows, which indicated that Phase 2 remained the largest driver of the clinical failure for anticancer drug development[50]. On the other hand, in contrast to the clear increase of P3SR from 37.1% to 57.7% (as provided in Supplementary Fig. S6), P1SRs dramatically declined from 67.8% to 37.3%. Such declines in P1SRs indicated an increasing risk in the early clinical development of innovative targeted drug and immunotherapy for cancer[51], which recently prompted the U.S. FDA *Oncology Center of Excellence* (OCE) to launch *"Project Optimus"* focusing on the dose optimization for Phase 1 trial of anticancer therapy discovery[52]. In addition, the increase of P3SR accompanied by declines of P1SR identified in this study might indicate that the early clinical evaluation of current pharmaceutical industry became increasingly thorough, which might help to prevent the costly late-stage (especially Phase 3) failure[22].

Anticancer drugs collected into this study consisted of the largest proportion among other disease classes, and it was thus essential to investigate the impacts of oncologic therapies on the ClinSRs of all CDPs. In this study, the comparison of ClinSRs between oncologic (red) and non-oncologic (blue) CDPs was described in Fig. 4a (yellow background). As demonstrated, the CDPs-based OSRs of anticancer drug (oncologic) were consistently lower than that of the non-anticancer one (non-oncologic). Particularly, although P1SRs of oncologic and non-oncologic CDPs were found comparable at the beginning of 21st century, the oncologic P1SRs showed continuous decline in recent years, which was different from the trend of slight increase of non-oncologic P1SRs; when it came to P2SR, the evolving trends of oncologic and non-oncologic CDPs were almost identical with the non-oncologic P2SR consistently higher than oncologic ones; in contrast to the declining trend of non-oncologic P3SR, the oncologic P3SR elevated over time. Moreover, the comparison of ClinSRs between oncologic (red) and non-oncologic (blue) MEs was also described in Fig. 4a (blue background). As shown, the MEs-based OSR, P1SR and P3SR (between anticancer and non-anticancer drugs) followed the trends generally similar to that of the CDPs-based ones, while the P2SR of oncologic MEs was higher than that for non-oncologic ones in the early 21st century (different from the CDPs-based result). In other words, the CDPs-based and MEs-based analyses revealed that in most cases the ClinSRs of oncologic drugs were lower than that of non-oncologic ones, but the P3SRs of oncologic drug were identified higher comparing with non-oncologic one in recent time-windows. In sum, great impact of oncologic therapies on ClinSR was observed.

Assessing the ClinSRs for drugs treating neurological disease

The dynamic ClinSRs evaluated using the CDPs of *neurological disease* collected to this analysis were explicitly described in Supplementary Fig. S7. As shown, the OSRs had been declining in the early 21st century by hitting the bottom with an extremely low OSR of 3.5% in 2008–2016, and, then, experienced a slow but clear increase in recent years. As reported, such low OSRs of neurological diseases primarily originated from the difficulty in crossing the *blood-brain barrier*, notoriously unpredictive animal models, and poor understanding of complex CNS condition[53]. To deal with these issues, advances in drug delivery systems[54], strategies to promote successes in translating preclinical outcome in animal model to the clinic[55], and technologies elucidating mechanisms underlying neurological diseases[56] were widely used in the past decade. All these efforts might collectively contribute to the steady elevations in the OSRs of neurological diseases in recent years (offered in Supplementary Fig. S7). Moreover, the evolution of *phase success rate* was also shown in Supplementary Fig. S7. Comparing with P1SR and P2SR, there were clear elevations in recent P3SR, which contributed the most to the recent elevation of OSR.

Assessing the ClinSRs for drugs treating infectious/parasitic disease

The dynamic ClinSRs evaluated based on the CDPs of *infectious diseases* collected for this study were explicitly described in Supplementary Fig. S8. As shown, the OSRs had been declining over time, and hit the bottom with a very low OSR of 2.6% in the latest time-window 2015–2023. At the beginning of this century, the OSR of infectious disease was more than two times as many as that of oncology, while its OSRs in recent years became comparable to that of oncology, which documented a dramatic decline in its ClinSR. As reported, the development of anti-infective drug had changed its pivot from non-host targets to the host ones, which led to increasing development difficulty and might therefore result in the dramatic decline of clinical trial success[48].

The drugs/candidates for treating COVID-19 had been frequently tested in clinical trials in recent years, which consisted of a large proportion of anti-infective drugs, and it was therefore essential to investigate the impact of COVID-19 therapies on the ClinSR of all anti-infective drugs. In this study, the comparison of ClinSRs between the CDPs of COVID-19 and that of infectious disease excluding COVID-19 was conducted, and the findings were provided in Fig. 4b. As illustrated, there was no substantial difference in P1SRs and P2SRs between the studied two groups of CDPs. However, dramatic variation was observed in P3SR which provided a substantially lower rate of success (6.1%) for COVID-19 CDPs than that (34.7%) of non-COVID-19 CDPs. Moreover, such a low P3SR further resulted in a low OSR (0.7%) of COVID-19 CDPs comparing with that (4.4%) of non-COVID-19 CDPs. Extra analyses of the impact of FDA, EMA and NMPA on the ClinSRs of anti-COVID-19 drugs were conducted. The resulting P3SRs presented slight variations among FDA (6.1%), EMA (8.1%) and NMPA (8.0%), which in turn brought about gentle fluctuation in their OSRs (0.7%, 0.9% and 0.9%, respectively).

Moreover, an in-depth analysis differentiating the industry-sponsored COVID-19 CDPs from the non-industry-sponsored ones (e.g., academic trials) were performed. As shown in Fig. 4b, no substantial difference in P1SRs and P2SRs between all COVID-19 CDPs and

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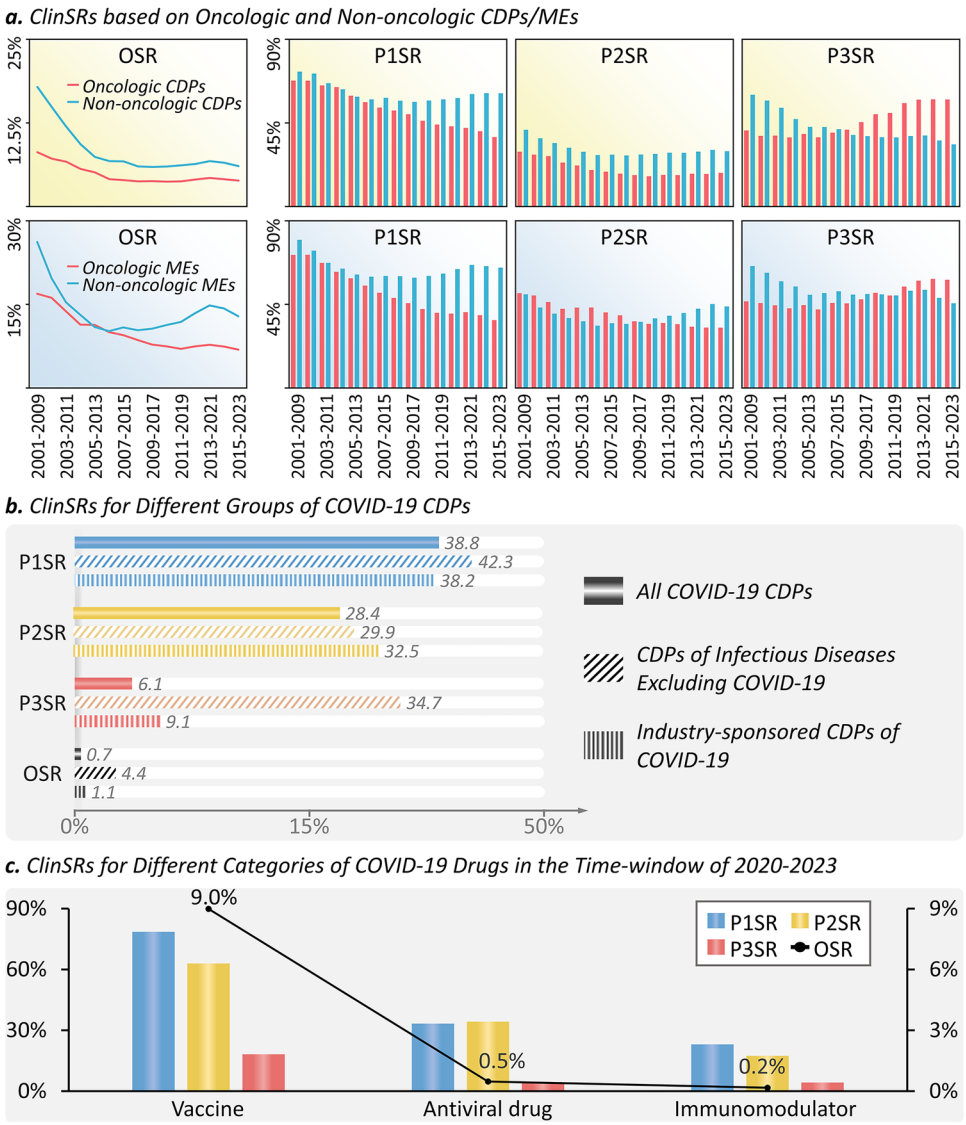

Fig. 4 | Comparing ClinSRs among disease classes based on CDPs & MEs. **a** Comparing the ClinSRs between the drugs for oncologic and non-oncologic diseases based on CDP and ME. **b** Comparing the ClinSRs among three different CDP groups in time-window 2015–2023, including all COVID-19 CDPs, CDPs for infectious disease excluding COVID-19, and industry-sponsored CDPs for COVID-19. **c** Comparing the ClinSRs among different categories of anti-COVID-19 drugs in 2020-2023 (vaccine, antiviral drug and immunomodulator). Source data are provided as a Source Data file. CDPs clinical development programs, ME molecular entity, ClinSRs clinical trial success rates, OSRs overall success rates, P*n*SR phase *n* success rate.

industry-sponsored COVID-19 CDPs was observed. However, comparing with the P3SR of all COVID CDPs (6.1%), that of the industry-sponsored COVID CDP (9.1%) was higher, but remained significantly lower than that (34.7%) of non-COVID-19 infectious CDPs. Furthermore, such a low P3SR further led to low OSRs of both all COVID-19 CDPs (0.7%) & industry-sponsored COVID-19 CDPs (1.1%) comparing with that of the non-COVID-19 infectious CDPs (4.4%). All the results indicated that the OSRs of all and industry-sponsored anti-COVID drugs were substantially lower than that of anti-infectious but non-COVID drugs, and the non-industry sponsored anti-COVID clinical trials were found more likely to end in failure. In the meantime, all anti-COVID-19 drugs approved so far were shown in Supplementary Table S3, and all anti-COVID-19 drugs analyzed in this study were also categorized into three groups (antiviral drug, immunomodulator, and vaccine) to assess whether there was discrepancy among the ClinSRs of drugs in these three categories. As depicted in Fig. 4c, vaccine resulted in the highest ClinSR, and immunomodulator gave the lowest one.

Besides those three disease classes discussed above, the dynamic ClinSRs assessed based on the CDPs of eleven additional classes of disease (such as: *circulatory system disease*) defined by the WHO ICD-11 were explicitly offered in Supplementary Figs. S9–S19. The detailed values of the calculated P1SRs, P2SRs, P3SRs were described in Supplementary Tables S4–S6. Moreover, dynamic ClinSRs assessed based on the molecular entities (MEs) of all 14 disease classes defined by the WHO ICD-11 were also systematically described in Supplementary Figs. S20–S33. As illustrated, the MEs-based calculations (regardless of different diseases) tended to result in higher probabilities of success than the CDPs-based one (considering all indications), but their resulting time-dependent trends for the same disease class were highly similar with each other.

Similarity among disease classes identified based on their ClinSRs

To reveal the similarity among diseases in their ClinSRs across fifteen time-windows, the cluster analyses based on OSRs, P1SRs, P2SRs and

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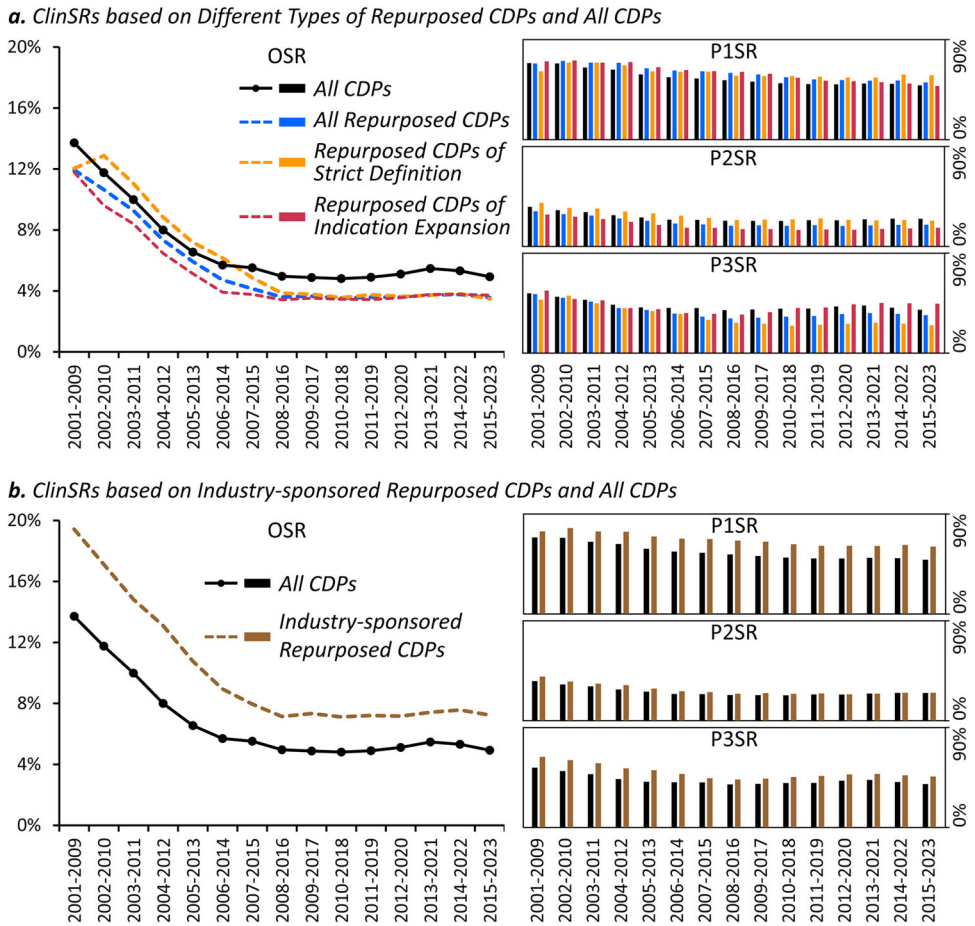

Fig. 5 | The dynamic *clinical trial success rates* (ClinSRs) for the repurposed CDPs calculated in the research. a The ClinSRs evaluated based on the CDPs of *all repurposing* (dash-line & bar in blue), *strictly-defined repurposing* (dash-line & bar in orange) and *indication expansion* (dash-line & bar in red) together with those of all CDPs (solid-line & bar in black). **b** ClinSRs assessed using industry-sponsored repurposed (dash-line & bar in brown) and all (solid-line & bar in black) CDPs. Source data are provided as a Source Data file. P*n*SR phase *n* success rate, OSR overall success rate.

P3SRs were carefully conducted, and corresponding results were provided in Supplementary Figs. S34–S37. Particularly, disease classes were *first* ranked based on ClinSRs across 15 time-windows, and a complete linkage hierarchical clustering was *then* calculated using the ranking results based on *Euclidean* distances. Taking the clustering based on OSR (Supplementary Fig. S34) as example, two clustering groups were discovered with six disease classes (BLOOD, MUSKE, IMMUN, METAB, GENIT & VISAL) at the bottom and others (CACER, CIRCU, NEURO, DIGST, RESPR, INFEC, SKINS & OTHER) on the top. Particularly, although BLOOD was grouped together with the immune system diseases (IMMUN) and musculoskeletal system/connective tissue disease (MUSKE), its OSRs across time-windows (as described in Supplementary Table S2) were higher than those of both IMMUN and MUSKE. BLOOD was found with the steadily higher OSR than others. One of the possible reasons behind the high OSRs of BLOOD might be the fact that most (84.0%) of the BLOOD disease indications analyzed in this study were *hemophilia*, *anemia*, *thrombocytopenia*, and *blood protein deficiency*, the underlying biology of which had been well-characterized[57,58]. Furthermore, the drugs of BLOOD were more likely to reach the target tissues and therefore gave higher bioavailability, in contrast to other diseases in which the target tissues (such as brain) might be less accessible[59]. As described in Supplementary Fig. S34, oncology (CACER) and circulatory system disease (CIRCU) were found to be the typical disease class of the top group, which provided consistently the lowest OSRs across fifteen time-windows comparing with other disease classes.

Assessing & analyzing the dynamic ClinSRs for repurposed drugs

Drug repurposing is a strategy to discover new indication for drugs beyond their initial indication[60]. Given its characteristic of the less risk in safety, more rapid return on investment, and lower average cost after failure, the enthusiasm for drug repurposing was growing[61]. An appreciable number of pharmaceutical researchers held an optimistic attitude that drug repurposing was more likely to be successful than traditional ways of drug development[62]. Although the ClinSRs of repurposed drugs were quantitatively measured for certain disease[63], there remained a lack of systematic analysis on such point of view. There were two types of drug repurposing: the *strictly-defined repurposing* for the pursuit of unrelated disease indications, for example, from cancer to infection[61] and the *indication expansion* aiming at pursuing closely-related disease indications, commonly happened within a disease class, for instance, from one oncological disease to another[64]. Here, as illustrated in Fig. 5a, the ClinSRs for the CDPs of *all repurposing* (dash-line & bars in blue), *strictly-defined repurposing* (dash-line & bars in orange), and *indication expansion* (dash-line & bars in red) were explicitly provided. As described, the *strictly-defined repurposing* CDPs resulted in higher OSRs than all CDPs (a solid-line in black) in the early 21st century, but consistently lower OSRs in recent time-windows. Different from the *strictly-defined repurposing* CDPs, the *all repurposing* ones and *indication expansion* ones demonstrated a stably lower OSRs compared with all CDPs. In other words, in recent time-windows, three types of drug repurposing (*all repurposing*,

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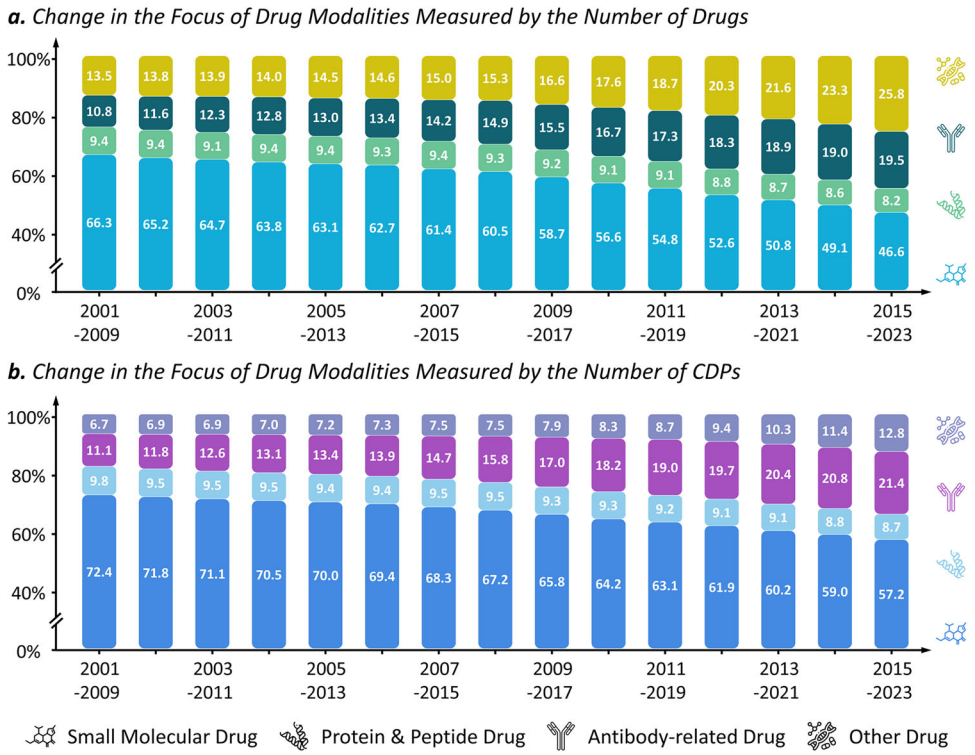

Fig. 6 | The change in the research focus of drug modalities over time. a Shifts in the research focuses of drug modalities measured by the numbers of clinically tested unique molecular entities. Percentage of small molecular drugs had been declining from 66.3% (the start of the 21st century) to 46.6% (now) with observable increase of the shares of antibody-related drugs (from 10.8% to 19.5%) and other drugs (from 13.5% to 25.8%). **b** The shifts in research focus of drug modalities measured by the total numbers of CDPs. The percentages of CDPs of small molecular drugs kept declining from 72.4% to 57.2% with a clear increase of the share of antibody-related drugs (from 11.1% to 21.4%) and others (from 6.7% to 12.8%). CDPs clinical development programs.

strictly-defined repurposing & indication expansion) gave similar success rates, which were consistently lower than all CDPs. This result was, from the perspective of ClinSR at least, contrary to the traditional "optimistic attitude" on the success of repurposed drugs. An extra study on the OSR of three classes of disease (neoplasm, neurology and infection) popular in drug repurposing[64,65] was performed, which identified a discrepancy among the OSRs of different disease classes. Particularly, in recent time-windows, the OSRs of drugs repurposed to neoplastic disease were relatively higher than that to the other two disease classes, but the OSRs of all three classes of disease were consistently lower than that of all disease (all CDPs in Fig. 5a). Additionally, the right side of Fig. 5a also illustrated the PSR for three types of repurposed drugs. As shown, the P1SRs of repurposed CDP were higher than that for all CDP in most cases, which was readily understandable since most of the repurposed drugs had been previously assessed for safety.

An in-depth analysis differentiating the industry-sponsored repurposed CDPs from non-industry-sponsored ones (e.g., academic trials) was further conducted to discover potential reasons behind the low ClinSRs of repurposed drugs. As provided in Fig. 5b, the OSRs and PSRs (particularly, P1SRs and P3SRs) of industry-sponsored repurposed CDPs (brown dash line) were identified to be consistently higher than that of all CDPs (black line with dots). Such results indicated that the low success rate of repurposed drugs might come from high proportion of academic investigators undertaking drug repurposing activities, which could dramatically pull down the success rates in pharmaceutical R&D[64]. An extra analysis of the clinical trial data used in this work was further conducted, which found that the academia tended to devote efforts to challenging, high-risk, and less profitable indications (*Creutzfeldt-Jakob disease*, for example, has so far only been clinically assessed by academia). These discoveries aligned with previous works claiming that (*a*) academic researchers tended to engage in cutting-edge high-risk projects, rather than address the real-world medical needs, making the corresponding projects less attractive to commercial investments[66]; (*b*) compared with the academic researchers, pharmaceutical companies accumulated much richer real-world data, expertise, and experience in evaluating their projects, allowing for more efficient resource allocation[67]. In sum, the findings asked for a careful evaluation of potential challenge and an effective avoidance of blind exploration during academia-driven drug repurposing.

Diverse and dynamic ClinSRs measured based on drug modalities

Drug modality had also been considered as one of the risk contributors to the success rate of drug development[11]. Small molecular drug (SMD) had long been the dominant modality and newer ones (such as antiboday-related drug) had also been added to the drug development toolbox[68]. As demonstrated in Fig. 6a, a clear shift in the research focus on various drug modalities was observed based on assessing the number of unique molecular entities in clinical trial. Particularly, during the past two decades, the percentages of SMDs kept declining from 66.3% (at the beginning of 21st century) to 46.6% (currently) with observable increase of the shares of antibody-related drugs (ARDs) (from 10.8% to 19.5%) and other drugs (from 13.5% to 25.8%, especially RNA-based therapies, cell therapies, gene therapies, etc.). Moreover, as illustrated in Fig. 6b, a shift in the research focus on various drug modalities was also observed based on assessing the number of CDPs. Particularly, in the past two decades, the percentage of CDP of SMDs kept declining from 72.4% (early 21st century) to 57.2% (currently) with clear increase of the shares of ARDs (from 11.1% to 21.4%) and others (from 6.7% to 12.8%).

In this study, the analyses on four types of major drug modality, including: SMD, ARD, protein & peptide drug (PPD) and other drug (OTH), were conducted, and their ClinSRs were described in Supplementary Table S7, and separately shown in Supplementary Figs. S38–S41. As depicted in Supplementary Table S7, the OSRs of ARD were higher than those of other modalities in recent decade, while the OSRs of PPD for the early 21st century surpassed those of the others. The OSRs of OTH (a mixture of highly diverse classes of drug, such as: RNA therapy and cell therapy) remained the lowest across fifteen time-windows. As the most well-established drug modality, three factors of SMD were considered as the primary reason leading to its failure, including poor physicochemical property, unmeaningful efficacy of the chosen targets and constant turmoil of strategy variation with pharmaceutical companies[68]. With the increasing elucidation of the molecular mechanism underlying the disease pathogenesis, an extensive growth potential of ARDs was also highly anticipated[69]. Because of the unique advantages of different drug types, current pharmaceutical industry tended to adopt a broad mixture of drug modalities for disease treatment[68].

Furthermore, the dynamic ClinSRs measured based on molecular entities (MEs) of four types of major drug modality were also systematically described in Supplementary Figs. S42–S45. As illustrated, the MEs-based calculations (regardless of different diseases) tended to result in higher probabilities of success than the CDPs-based one (considering all indications), but their resulting time-dependent trends for the same drug modality were highly similar with each other.

Evaluating the potential biases introduced by the analyzed datasets

In this study, ClinicalTrials.gov and Drugs@FDA were two databases used for analyzing ClinSR, and the potential biases introduced by the reliance on these databases were further assessed.

Assessing the bias introduced by the drugs not aiming at US approval

The first potential bias may come from the inclusions of early stage academic pursuits and trials intended to bring candidates outside the market of United States. In other words, it was necessary to reanalyze the ClinSR of drugs that specifically targeting US approval, but no such information could be retrieved from ClinicalTrials.gov and Drugs@FDA. To address this issue, we integrated the information of country, where a drug was developed in for diseases, from the *Pharmaprojects* database into this study, which helped to determine whether a drug was intended for US approval or not. As a result, about 22.5% of all industry-sponsored CDPs were discovered to be developed outside US. Based on the data of *Pharmaprojects* and ClinicalTrials.gov, ClinSRs for those drugs targeting US approvals were calculated. As shown in Supplementary Fig. S46a, the dynamic OSRs for all CDPs, industry-sponsored CDPs, and the CDPs aiming at US approvals were shown using *black solid-line with dots*, *green dash-line with diamonds*, and *blue dash-line with triangles*, respectively. It could be observed that the OSRs for CDPs aiming at US approval were obviously larger than that of all CDPs and slightly larger than that of industry-sponsored CDPs. Meanwhile, the OSRs for the CDPs aiming at US approvals revealed a declining trend over time, with relative stability observed in recent years, which gave a descending trend very similar to that for all CDPs and that for industry-sponsored CDPs (as illustrated in Supplementary Fig. S46a).

Furthermore, based on the analysis above, the corresponding bias of data inclusion was corrected using the data of *Pharmaprojects*, and the OSRs for CDPs aiming at US approval were given in Fig. 2a and Supplementary Fig. S47a (highlighted using the *grey dash-line with triangle*). As provided in Fig. 2a, the OSR for CDPs aiming at US approval (*grey dash-line with triangle*) had been declining over time (this trend aligned well with that for all CDPs), and remained stable around 8.8% in recent years (with deviations between black and grey lines around 3.7% in recent time-windows). Similar ClinSR analysis was conducted for MEs aiming at US approval, and the OSRs for MEs aiming at US approvals were illustrated in Fig. 2b and Supplementary Fig. S47b (highlighted using the *grey dash-line with triangle*). As depicted in Fig. 2b, the OSR for the MEs aiming at US approval had been declining over time (this trend aligns well with that for all MEs), and remained stable around 14.0% in recent years (with differences between black and grey line around 2.2% in recent time-windows). As a result, the bias of data inclusion was further corrected systematically. Particularly, the OSRs for CDPs aiming at US approval were illustrated using *grey dash-line with triangle* in Supplementary Figs. S48–S61 for each disease class and Supplementary Figs. S62–S65 for drug modalities, and those for MEs aiming at US approvals were provided using *grey dash-line with triangle* in Supplementary Figs. S66–S79 for disease classes and Supplementary Figs. S80–S83 for drug modalities. As provided in the figures, the OSRs for CDPs/MEs aiming at US approval were consistently higher than that for all CDPs/MEs, but the trends of these two types of OSRs (highlighted using a *black solid-line with dots* & a *grey dash-line with triangle*) were highly similar. Furthermore, the OSRs for all CDPs/MEs (the *black solid-lines with dots*) were also depicted in those figures as references for indicating the deviation from that aiming at US approval (*grey dash-lines with triangle*). Both types of OSRs (*black solid-line* and *grey dash-line*) were systematically depicted in the corresponding figures here.

Assessing the bias introduced by the incomplete drug discontinuations

The second potential bias may originate from the non-mandatory clinical trial registration before 2007, which might overestimate ClinSR at the early 21st century. In other words, it was necessary to measure the 'survivor bias' introduced by the incomplete inclusion of discontinuation data for drugs, especially those before year 2007. To address the problem, we incorporated the knowledge of discontinued time, diseases and phase for drugs from the database of *Pharmaprojects* into this analysis. Particularly, the discontinuation information described by the *Pharmaprojects* database for a total of 4707 unique molecular entities that had ever entered clinical trial were accumulated, and the OSRs were then calculated by adding the collected discontinuation data into the analyses. As shown in Supplementary Fig. S46b, the dynamic OSRs before and after the correction of "survivor biases" were provided using a *blue dash-line with triangles* and a *purple dash-line with diamonds*, respectively. As illustrated, for those time-windows containing data prior to 2007, the OSRs exhibited clear decline with their deviation ranging from 0.7% to 4.8%. The magnitude of the declines across each time-window became increasingly smaller as the number of years before 2007 decreased. Additionally, it was also observed that the OSRs after the correction of "survivor bias" (*purple dash-line with diamonds*) for the time-windows after 2007 were almost identical to that before the correction (*blue dash-line with triangle*). These findings highlighted the necessity of correcting "survivor biases" to achieve unbiased direct comparison among time-windows.

Furthermore, based on the analysis above, the corresponding bias of data inclusion was corrected by an approach of *collective adjustment*, which not only focused on the CDPs/MEs aiming at US approval but also corrected the "survivor biases" of incomplete drug discontinuation. In this study, the adjustment was applied to Fig. 2a, leading to the OSRs after collective adjustment (*purple dash-line with diamond*, which were identical to the purple line demonstrated in Supplementary Fig. S46b), and the PSRs for CDPs after the adjustments were also offered in Supplementary Fig. S47a (shown by bars in blue, yellow, and red). One thing we would like to discuss further was about the prior studies reporting the OSRs of 10.4% for 2003–2011[2], 9.6% for 2006–2015 (*BIO*, https://www.bio.org/), and 7.9% for 2011–2020 (*BIO*, https://www.bio.org/). As offered in Fig. 2a, the OSRs after the

collective adjustments equaled to 12.3% (2003–2011), 9.2% (2007–2015) and 8.4% (2011–2019), which were comparable to those from the prior studies. Taking the 2011–2020 window as example, the P2SRs obtained in this study were 28.4% for 2012–2020 and 28.8% for 2011–2019, which were close to that (28.9%) of *BIO*; the P3SRs obtained in this study equaled to 53.0% for 2012–2020 and 50.4% for 2011–2019, remaining comparable to that (52.4%) of *BIO*. Similar analysis was conducted for MEs after the collective adjustment, and the resulting OSRs were added to Fig. 2b (given by *purple dash-line with diamond*), and the corresponding PSRs were also offered in Supplementary Fig. S47b (bars in blue, yellow, and red). As shown in Fig. 2b, the OSRs for MEs after collective adjustment (*purple dash-line with diamond*) had been declining over time, with a relative stability in recent windows, which aligned with that for all MEs (*black solid-line with dot*). Furthermore, although the CDPs- and MEs-based OSRs were discovered continuously declining over time, the MEs-based ones were found consistently higher than the CDP-based ones (as shown in Supplementary Fig. S84a), and the MEs-based P2SRs and P3SRs were higher than the CDPs-based ones (as provided in Supplementary Fig. S84b). In other words, the CDPs-based assessment (considering all indications) tended to result in lower probabilities of success than the MEs-based one (regardless of the different indications), aligning well with the findings for all CDPs (as described in Supplementary Fig. S5).

Correcting the bias of data inclusions using the collective adjustment

Based on the above analysis, the survivor bias in collected data was further corrected. Particularly, the OSRs for CDPs after the collective adjustment were shown by *purple dash-line with diamond* in Supplementary Figs. S48–S61 for disease classes and Supplementary Figs. S62–S65 for drug modalities, and those for MEs after collective adjustment were provided using *purple dash-lines with diamonds* in Supplementary Figs. S66–S79 for disease classes and Supplementary Figs. S80–S83 for drug modalities. Additionally, the PSRs for CDPs after collective adjustment were shown by *blue*, *yellow*, and *red bars* in Supplementary Figs. S48–S61 for disease classes and Supplementary Figs. S62–S65 for drug modalities, and those for MEs after the adjustment were shown by *blue*, *yellow*, and *red bars* in Supplementary Figs. S66–S79 for disease classes and Supplementary Figs. S80–S83 for drug modalities. As shown in these figures, for the vast majority of the disease classes (or drug modalities), the downward magnitude of the *purple dash-line* (indicating the OSRs after collective adjustment) relative to the *grey dash-line* (denoting the OSRs aiming at US approval) in the time-windows before 2007 were larger than that in the time-windows after 2007. Furthermore, the OSRs for all CDPs/MEs (a *black solid-line with dots*) and for CDPs/MEs aiming at US approval (the *grey dash-line with triangle*) were also shown in those figures as the references for indicating the deviations from that for CDPs/MEs after the collective adjustments (*purple dash-lines with diamond*). In other words, to have a holistic view of ClinSRs, all three types of OSRs were drawn in the figures of this study. Moreover, the OSRs of 14 disease classes after collective adjustment across 15 windows were systematically described in Table 2, and the ClinSRs of 4 drug modalities after collective adjustment were also shown in Table 3.

In our study, this collective adjustment was further applied to correct those findings in Figs. 4 and 5, which could help to give an in-depth comparison of (*a*) ClinSRs between oncologic and non-oncologic CDPs/MEs, (*b*) ClinSRs among different groups of COVID-19 CDPs, and (*c*) ClinSRs among different classes of drug repurposing. Therefore, the adjusted versions of Figs. 4 and 5 were illustrated in Supplementary Fig. S85 and Supplementary Fig. S86, respectively and discussed below.

Comparison of ClinSRs between oncologic (red) and non-oncologic (blue) CDPs after *collective adjustments* was shown in Supplementary Fig. S85a (yellow background). The CDPs-based OSRs of anticancer drug (oncologic) were consistently lower than that of the non-anticancer one (non-oncologic). Particularly, although P1SRs and P2SRs of oncologic and non-oncologic CDPs were found comparable at the beginning of 21st century, the oncologic P1SRs and P2SRs showed continuous decline in recent years, which were different from the trend of slight increase of non-oncologic P1SRs and P2SRs; in contrast to the gradually declining trend of non-oncologic P3SRs, the oncologic P3SRs increased in recent time-windows. In summary, the above trends of ClinSRs (both OSRs & PSRs) for oncologic CDPs after *collective adjustment* were highly similar to those for all oncologic CDPs (before the adjustment, which were previously shown in Fig. 4a).

Furthermore, the comparison of ClinSRs between oncologic (red) and non-oncologic (blue) MEs was also described in Supplementary Fig. S85a (blue background). For oncologic MEs, their OSR trend is like that of CDPs, both exhibiting a continuous downward trend. For non-oncologic MEs, their OSR values follows a trend similar to that of CDPs, characterized by an initial decline followed by subsequent increase. Notably, in the early 21st century, ME-based OSR of oncologic drugs was higher than that of non-oncologic ones. However, this was reversed in recent windows, with oncological drugs exhibiting lower OSRs than the non-oncological ones—a key divergence between CDPs-based and MEs-based results. Trends of MEs-based P1SRs and P2SRs are largely consistent with those of CDP-based ones. The main divergence, however, lies in the P2SR: while oncologic CDPs had lower P2SRs than the non-oncologic ones, MEs-based calculations initially gave a higher P2SR for oncologic drugs. Such discrepancy may explain why the oncologic drugs exhibited higher OSR than non-oncologic ones at the beginning of 21st century. Regarding P3SR, there is little difference between ME-based and CDP-based results for oncologic drug. In contrast, non-oncologic ones showed distinct MEs-based trend for P3SRs—initially declining, then rising, before declining again—unlike the steady decrease observed in CDP-based analysis. In sum, the CDPs-based and MEs-based analyses identified that in recent years the OSRs of oncologic drugs were lower than that of non-oncologic ones, but the P3SRs of oncologic drugs were found higher than those of non-oncologic ones in two most recent time frames (2014–2022 & 2015–2023).

The ClinSRs after the *collective adjustment* for two groups of CDPs were analyzed: the COVID-19 CDPs and CDPs of infectious diseases excluding COVID-19. As depicted in Supplementary Fig. S85b, there was no substantial difference in the P2SRs between the studied two groups. However, 10.0% difference was revealed in their P1SRs, and dramatic variation was also observed in P3SR which described a substantially lower rate of success (12.5%) for COVID-19 CDPs than that (46.0%) of non-COVID-19 CDPs. Moreover, such low P3SR further led to a low OSR (1.1%) of COVID-19 CDP compared with that (5.9%) of non-COVID-19 CDP. Many anti-COVID-19 CDPs have entered into Phase 3[42], but most of them ended in failures. In other words, although there are anti-COVID-19 drugs approved in very short time frame, it is apparent that such success came at a high cost of huge number of clinical failures. Several possible reasons contributing to the low ClinSRs of anti-COVID-19 drugs were reported. *First*, the problem of poorly designed/reported anti-COVID clinical study became serious during pandemic[70]. Specifically, many small-scale trials lacked statistical power to generate meaningful results, and were abandoned due to futility. *Second*, the emergency use authorization (EUA) for COVID-19 treatment often involved incomplete approval processes, which might result in the premature clinical trials[71]. For example, clinical trials on chloroquine & hydroxychloroquine were halted after their revocations of EUA. All these problems might collectively affect P3SRs and in turn lead to the low OSRs in Supplementary Fig. S85b, which called for the establishment of stricter design standards and implement of innovative trial design strategy (e.g., adaptive platform trial) for clinical evaluation in the event of a future pandemic[72].

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Table 2 | The OSRs after the collective adjustment for all CDPs collected for this study and the CDPs of certain disease class (14 classes defined by WHO ICD-11) calculated across fifteen nine-year time-windows

Disease class	2001–2009	2002–2010	2003–2011	2004–2012	2005–2013	2006–2014	2007–2015	2008–2016	2009–2017	2010–2018	2011–2019	2012–2020	2013–2021	2014–2022	2015–2023
All	16.7%	14.3%	12.3%	11.1%	9.8%	8.9%	9.2%	8.6%	8.7%	8.6%	8.4%	8.6%	8.9%	8.6%	8.1%
01 INFEC	20.7%	20.4%	19.6%	17.1%	11.9%	10.8%	13.4%	12.3%	10.3%	8.5%	7.1%	7.1%	8.0%	6.0%	3.9%
02 CACER	15.2%	13.2%	11.6%	10.4%	9.4%	7.8%	7.4%	6.7%	6.7%	6.3%	6.0%	6.1%	6.0%	5.8%	5.7%
03 BLOOD	59.9%	58.0%	36.9%	40.7%	38.4%	32.4%	33.7%	34.8%	37.4%	35.5%	35.9%	41.9%	39.3%	32.6%	34.1%
04 IMMUN	35.1%	43.3%	33.2%	26.4%	23.7%	18.7%	15.3%	12.7%	14.6%	14.4%	11.5%	12.2%	15.3%	15.6%	15.0%
05 METAB	17.4%	14.7%	10.3%	10.0%	8.8%	8.6%	9.8%	10.0%	10.4%	12.0%	12.2%	12.2%	14.3%	13.3%	12.8%
06 NEURO	17.3%	12.4%	10.3%	7.8%	6.5%	5.5%	5.3%	6.1%	6.7%	6.6%	8.7%	10.4%	10.6%	13.0%	13.0%
07 VISAL	20.3%	18.1%	14.0%	14.0%	10.5%	10.8%	11.1%	11.1%	11.8%	11.2%	9.2%	9.3%	11.0%	10.8%	11.2%
08 CIRCU	10.3%	8.6%	6.5%	7.0%	7.4%	7.9%	8.9%	7.3%	7.4%	8.6%	6.6%	5.9%	7.1%	5.8%	4.7%
09 RESPR	9.6%	9.0%	8.9%	7.7%	7.4%	7.8%	7.5%	6.8%	6.3%	6.0%	6.2%	5.5%	7.8%	7.2%	7.0%
10 DIGST	8.6%	8.4%	10.6%	11.2%	12.1%	9.7%	10.5%	8.9%	10.1%	12.6%	13.4%	12.1%	12.5%	12.6%	9.3%
11 SKINS	8.4%	13.3%	9.9%	7.4%	5.1%	7.3%	10.6%	9.6%	10.6%	12.5%	12.0%	12.3%	13.8%	13.9%	15.0%
12 MUSKE	24.8%	19.7%	18.0%	17.6%	16.3%	14.0%	13.1%	11.6%	9.9%	9.8%	10.0%	8.9%	8.4%	8.1%	8.7%
13 GENIT	14.4%	10.9%	7.8%	5.8%	9.4%	12.2%	11.5%	13.3%	15.0%	16.6%	19.1%	21.2%	15.7%	8.8%	8.1%
14 OTHER	13.3%	9.7%	12.3%	10.7%	10.3%	9.9%	11.7%	11.0%	10.8%	9.1%	7.8%	10.8%	11.0%	10.1%	8.5%

All all diseases; INFEC: Infectious/parasitic disease; CACER: Oncology; BLOOD: Blood/blood-forming organs disease; IMMUN: Immune system disease; METAB: Endocrine, nutritional or metabolic diseases; NEURO: Neurology; VISAL: Visual system disease; CIRCU: Circulatory system disease; RESPR: Respiratory system disease; DIGST: Digestive system disease; SKINS: Skin disease; MUSKE: Musculoskeletal system/connective tissue disease; GENIT: Genitourinary and sexual related disease; OTHER: Other disease.

Table 3 | The *clinical trial success rates* (ClinSRs, both *overall success rate* and *phase success rate*) after the collective adjustment for the CDPs of four major types of drug modalities

Drug Modality		2001–2009	2002–2010	2003–2011	2004–2012	2005–2013	2006–2014	2007–2015	2008–2016	2009–2017	2010–2018	2011–2019	2012–2020	2013–2021	2014–2022	2015–2023
OSR	SMD	15.1%	12.4%	10.6%	9.4%	8.7%	7.8%	7.8%	7.3%	7.4%	7.4%	7.4%	7.6%	7.7%	7.5%	7.2%
	ARD	24.4%	23.3%	22.5%	22.8%	18.2%	14.8%	15.5%	14.1%	13.6%	12.6%	12.4%	12.5%	13.2%	13.1%	12.0%
	PPD	33.1%	27.6%	21.9%	19.8%	17.4%	18.1%	18.0%	16.1%	15.1%	14.0%	12.9%	12.3%	11.5%	9.9%	9.2%
	OTH	1.5%	7.1%	4.7%	3.9%	2.8%	3.7%	4.1%	4.5%	5.3%	5.2%	4.9%	5.4%	6.5%	5.9%	5.8%
P1SR	SMD	70.1%	70.4%	67.3%	67.6%	66.7%	64.9%	64.4%	64.9%	64.3%	62.0%	61.0%	61.0%	60.5%	61.6%	59.9%
	ARD	67.9%	69.2%	72.8%	71.9%	66.9%	64.5%	63.6%	58.6%	58.6%	56.5%	52.9%	51.5%	52.3%	51.9%	52.9%
	PPD	80.4%	74.7%	70.0%	70.1%	69.0%	66.2%	69.6%	64.4%	63.1%	63.1%	64.8%	63.5%	62.2%	61.7%	60.1%
	OTH	73.0%	69.4%	62.5%	56.6%	48.4%	45.2%	44.9%	45.2%	45.7%	49.5%	48.4%	45.6%	47.5%	45.0%	48.0%
P2SR	SMD	37.6%	33.1%	30.8%	29.7%	29.1%	27.0%	27.2%	26.6%	26.4%	26.1%	26.3%	25.9%	26.6%	26.4%	26.6%
	ARD	47.5%	46.6%	45.6%	45.2%	41.1%	38.7%	37.5%	36.1%	35.0%	34.0%	34.9%	33.9%	35.1%	35.8%	33.7%
	PPD	54.6%	50.4%	47.7%	44.1%	42.9%	44.6%	42.5%	43.2%	41.6%	39.9%	38.2%	37.2%	33.3%	32.2%	30.5%
	OTH	37.3%	40.7%	34.0%	33.1%	26.3%	25.7%	25.8%	26.6%	27.9%	25.9%	25.8%	27.1%	28.8%	29.9%	26.8%
P3SR	SMD	57.0%	53.4%	51.0%	46.9%	44.9%	44.5%	44.6%	42.2%	43.5%	45.7%	46.4%	48.0%	47.6%	46.2%	45.1%
	ARD	75.6%	72.3%	67.9%	70.2%	66.2%	59.3%	65.1%	66.7%	66.4%	65.5%	67.0%	71.6%	72.0%	70.3%	67.1%
	PPD	75.6%	73.5%	65.5%	64.1%	58.7%	61.3%	60.9%	57.8%	57.4%	55.6%	52.2%	52.2%	55.4%	50.0%	50.0%
	OTH	5.6%	25.0%	22.2%	20.7%	21.9%	31.6%	34.9%	37.0%	41.9%	40.3%	38.9%	44.0%	47.7%	43.8%	44.9%

SMD small molecular drug, *ARD* antibody-related drug, *PPD* protein & peptide drug, *OTH* other drug, *OSR* overall success rate, *P1SR* phase 1 success rate, *P2SR* phase 2 success rate, *P3SR* phase 3 success rate.

In the meantime, all anti-COVID-19 drugs approved so far were shown in Supplementary Table S3, and all anti-COVID-19 drugs studied in this research were classified to three groups (antiviral drug, immunomodulator & vaccine) to assess whether there was discrepancy among the ClinSRs of drugs in these three groups. As given in Supplementary Fig. S85c, vaccine resulted in the highest ClinSRs, and immunomodulator gave the lowest ones. To explore the reason contributing to the differences above, a systematic literature review was also conducted. *On one hand*, several potential causes underlying the higher ClinSR of anti-COVID-19 vaccine were identified, which included: (*a*) the effective animal models constructed prior to the pandemic based on experiences gained from SARS-CoV[73], (*b*) the greatly reduced time frame for vaccine development by earlier antigen-design study on MERS[74], and (*c*) the availability of specific, sensitive, and meaningful clinical endpoints[75]. *On the other hand*, some of the potential factors underlying the low ClinSRs of immunomodulators were also found, which contained: (*a*) the great difficulty in determining key inflammatory mediator[76], (*b*) the undesired adverse reaction of non-specific immunosuppression[77], (*c*) the complexity in patient selection due to heterogeneous immune response[78].

The ClinSRs after *collective adjustment* for the CDPs of *all repurposing* (dash-line & bars in blue) and *repurposing of indication expansion* (dash-line & bars in red) together with those of all CDPs (a dash-line with diamonds & bars in purple) were depicted in Supplementary Fig. S86. As shown in Supplementary Fig. S86a, compared with the OSRs of all CDPs, those of "*all repurposing*" (as depicted using *blue dash-line*) and "*repurposing of indication expansion*" (as demonstrated by *red dash-line*) were higher in the early 21st century, but had recently become lower. Such results remained, from the perspective of *clinical trial success rates* at least, contrary to the traditional optimistic attitude on the success of repurposed drugs. This analysis highlighted the extremely low ClinSRs of anti-COVID-19 drugs revealed above, most of which were the repurposed ones[79]. Additionally, Supplementary Fig. S86b also offered the illustration of the PSRs for two types of repurposed drug. As shown, the P1SRs of repurposed CDPs were consistently higher than those for all CDPs in all timeframes, which is readily understandable since most of the repurposed drugs had been previously assessed for safety. Meanwhile, unlike remaining roughly comparable at the beginning of 21st century, in recent years, the P2SRs for two types of the repurposed CDP (*all repurposing* & *repurposing of indication expansion*) are substantially lower than those for all CDPs, which contributes most to the lower OSRs for repurposed CDPs than those for all CDPs in recent time-windows.

To investigate the potential causes underlying the low ClinSRs of repurposed drugs, a systematic literature review was performed with some important factors discovered. *First*, spurious data can be produced in initial screening assay. Because the approved drug can show promiscuous activity in screening assay, the evaluation of known drug in new assay can lead to false positive outcomes, undermining drug repurposing from the outset[64]. *Second*, the original mechanism of action may not be suitable for new indication. The relatively low costs of "*trial-and-error*" in repurposing had promoted a large number of trials to rush into clinical testing without a clear understanding of their targeted mechanisms, planting the seeds of failure for drug repurposing[80]. *Third*, a direct knowledge transfer may result in serious problem in clinical trial. Drug repurposing is seldom as trivial as performing a clinical trial for new diseases using the same strategy (dosage, formulation, and biomarker) as previously used, which makes it challenging to replicate the past success in new indication[81]. These discussions highlighted the possible cause leading to the failure of repurposed drug and in turn resulting in the low OSRs, and many approaches have thus been proposed to elevate the ClinSR of the repurposing programs[82], which asked for a prior evaluation in biological assay, a sound understanding of molecular mechanism, and a robust clinical design considering dosage, formulation & biomarker. All in all, although drug repurposing is attractive, available evidence suggests that cautions should be taken.

Construction of multi-functional platform for reporting ClinSRs

The ClinSRs of drugs were critical for both clinical researcher and pharmaceutical investor when making scientific and economic decisions[7]. However, the serious problem of "information lag" of previous studies could not effectively demonstrate the dynamic nature of ClinSR. Furthermore, considering the diverse research interests among researchers, a customized analysis on particular groups of drugs was highly demanded, but no such tool had been available. In this study, a multi-functional online platform, entitled "*ClinSR.org*", was thus constructed, which enabled a dynamic description of the ClinSR of any drug group of interests. Moreover, to cope with the problem of information lag, *ClinSR.org* was carefully designed to not only integrate all the data collected to this analysis, but also could be further updated for the coming decade. The characteristics of this online platform were explicitly described as follows.

An automated platform enabling the dynamic description of ClinSRs

As shown in Fig. 7a, a process enabling the automated data collection and ClinSR assessment was constructed. *First*, drugs and their corresponding clinical status were automatically collected from ClinicalTrials.gov and the U.S. FDA website by quarterly retrieving information using their *Application Programming Interface* (API). *Second*, diverse data affiliated to the newly-collected drugs were automatically retrieved by matching with three established databases (WHO ICD-11, DrugBank and TTD). *Third*, all the collected data were carefully reviewed and validated by well-trained pharmacologists and bioinformaticians in our team to guarantee the data quality, and were then integrated into the large pool of data collected to this analysis. *Finally*, the change of ClinSR among diverse time-windows was automatically calculated based on the latest collection of drugs, which was then updated and systematically visualized on the online website of *ClinSR.org*.

Personalized tool realizing the customized assessment of ClinSRs

As illustrated in Fig. 7b, a variety of strategies realizing the customized assessment of ClinSR based on the user's preference were described in *ClinSR.org*. Particularly, a user was allowed to assess the ClinSR for a particular class of disease or a specific modality of drug, and also evaluate the joint contribution of multiple disease classes or drug modalities to the success of clinical trial drugs. Moreover, the *ClinSR.org* enabled the assessment of ClinSR for any drug group of interest. Users can first upload a list of drugs (indicated by drug name, TTD drug ID, DrugBank accession, PubChem CID, etc.), and the ClinSR of these drugs will then be automatically calculated.

An integrated database reconstructing the CDP(s) for studied drug

Although ClinicalTrials.gov offered extensive clinical information on trial drugs, it lacked a clear summary of the CDP for each drug. Particularly, the information on ClinicalTrials.gov was offered in pieces, each of which focused only on one trial, which asked for the reconstruction of the entire CDP for each drug. As illustrated in Fig. 7c, the CDPs were therefore systematically reconstructed for each drug collected to this study, which were explicitly described in the section of "*Development Program Identification for a Drug of Distinct Disease*". Taking the drug *vilaprisan* (as described in Fig. 7c) as an example, it had been clinically tested for two disease indications (*endometriosis* and *uterine leiomyoma*). This led to two distinct CDPs for this specific drug, which were systematically described in *ClinSR.org* to facilitate the decision making for the researchers and investors in the fields of pharmaceutical sciences.

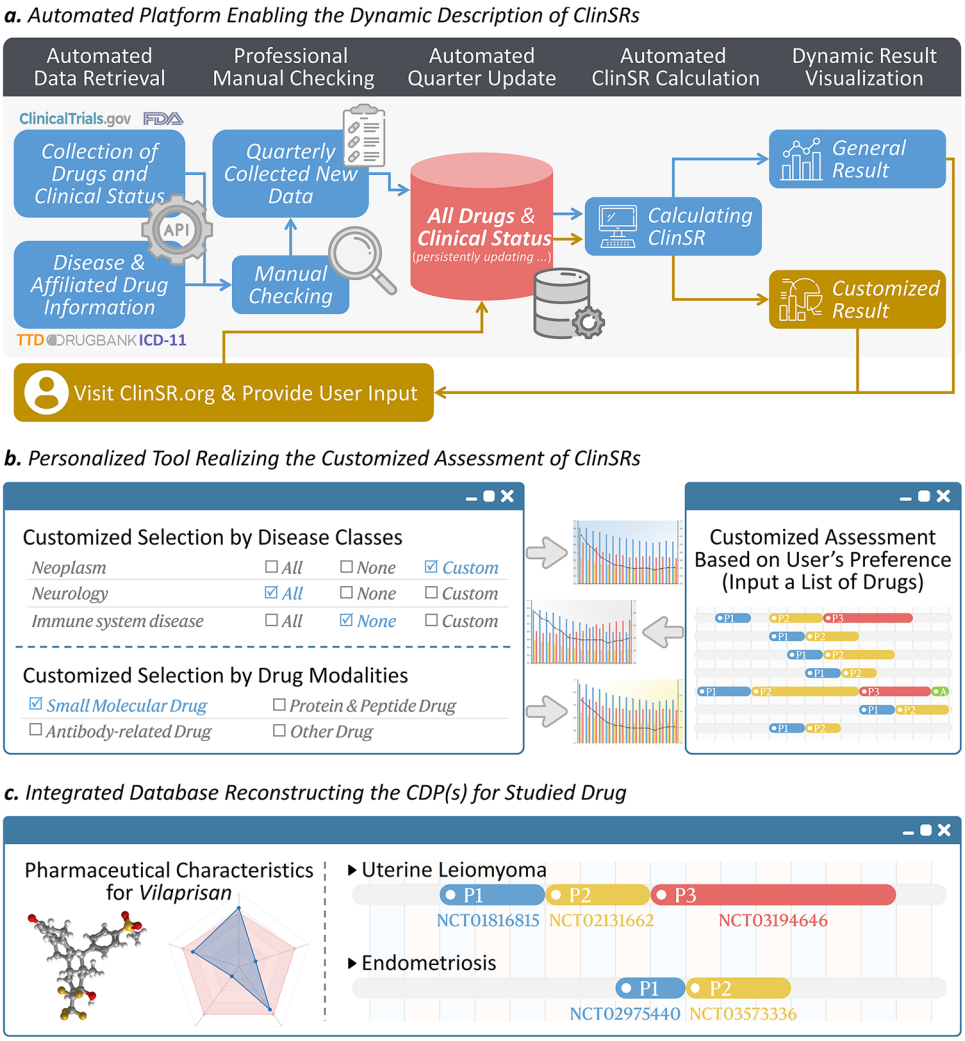

Fig. 7 | The multi-functional platform titled *ClinSR.org* developed in this analysis. The unique characteristics of *ClinSR.org* included: **a** automated platform enabling the dynamic description of ClinSRs; **b** personalized tool realizing the customized measurement of ClinSR; **c** integrated database reconstructing the CDP(s) for studied drug. New data and ClinSR assessment would be persistently updated to *ClinSR.org* for the coming decade. CDP clinical development programs.

Discussion

Data and conceptual limitations

The limitations of the data collected to this and any other data-driven studies should be discussed to make the readers be aware of the potential distortion of those data on results. In this study, all analyses were based on the clinical trial information from ClinicalTrials.gov, and any incomplete registration of trials to this database might affect the ClinSRs calculated in this study. Thanks to the scope and content expansion of mandatory clinical trial registration by *FDA Amendments Act* (FDAAA)[35] & trial registration policy of *International Committee of Medical Journal Editors* (ICMJE)[83], the data in ClinicalTrials.gov had become increasingly comprehensive, which can in turn improve the calculation accuracy of this work for reflecting the real trial successes.

However, as reported[83], the gaps in trial reporting databases/system & their associated policies (e.g., lack of mandatory registration requirement for Phase 1 trials) and unsatisfactory adherences to existing act/policy (e.g., late registration of new trial, incomplete or out-of-date registered trial information) suggested that there was room for improvement. Recent effort of ClinicalTrials.gov to remind users about the deadline for reporting trial result[84] and issuance of the FDAAA final rule on trial reporting[85] would fill some of those gaps and generate frameworks for monitoring policy adherence, but considerable work remained to be done[86], which might include effective enforcement from the regulators, open public audit of compliance for sponsor, and so on so forth. Moreover, in this study and many preceding articles[2,3,22], the concept "*success*" was used to describe the progression of drug in clinical development. However, in the real-world clinical use of drugs, a "*success*" should be collectively determined by multiple factors[46], such as the sales of drugs and the net patient benefits. In other words, this study focused on the clinical progression of drugs and calculated their success rate in clinical development. These calculated results should therefore not be directly considered as a full reflection of the real-world success of drugs.

The determination of the clinical progression for some stem-cell or other biologic-based projects was challenging, because they usually had the vague name in early phase trial and even the same product could vary from batch to batch. In other words, the reader was suggested to be aware of the potential distortion introduced to the assessment of ClinSRs by vague drug names.

Methodological limitations

Sensitivity analysis revealed that the selection of nine-year time-window was appropriate in term of the robustness of the calculated ClinSRs. However, with the increase of the time-window size (from nine to twelve), there remained subtle differences among the calculated success rates. This indicated that it was essential to maintain a

consistent window size, when comparing the ClinSRs, especially for the case requiring high resolution in success rate assessment. In other words, when it comes to a situation that the time-window size matters, the selection of nine-year time-window may not be appropriate enough, and our reported ClinSRs should thus be considered with caution. In other words, this reliance on the time-window of specific size cannot meet all analytical needs. Additionally, success rates were calculated for various cohorts, and the same trial may be counted in multiple windows, which made the studied time-windows not independent from each other.

Moreover, with the updates of ClinicalTrials.gov, the clinical status of some previous trials might be renewed to failures, which reminded us to be caution with the potential bias on clinical success rate due to boundary effect. Since insufficient time has passed to allow us to know that a trial has failed, the ClinSRs might undergo a bias in the latest time-windows.

Perspectives

Over the past two decades, it became obvious that the *productivity crisis* of pharmaceutical R&D remained a great challenge with the return-on-investment rates declining continuously[28]. This study provided a quantitative view on measuring the clinical trial success rate and reflecting how the *crisis* shifts over time, which observed that the success rates declined in the early 21st century, but then hit a plateau, and recently underwent a marginal but noticeable increase. The decline of success rate might be attributed to the exhaustion of easily achievable target/candidate, tightened regulatory standard, and rising competition that prioritized *first/best-in-class* drug[30–32], while the recent increase of success might be considered to be driven by advances in genetic knowledge and disease understanding, improved decision-making process in the R&D, and lower regulatory threshold[43]. Additionally, a significant increase of P3SR accompanied by a substantial decline of P1SR were discovered for the drugs treating oncologic diseases (illustrated in Supplementary Fig. S48). A similar but milder trend for both P3SR and P1SR was also identified for all drugs (as described in Supplementary Fig. S47a), which highlighted that there may be an extensive positive contribution of anticancer drug to the success of overall drug development. Furthermore, as depicted in Supplementary Fig. S50, the OSRs of anti-infective drugs in the last two time-windows were remarkably low (6.0% & 3.9%). It is of great interest to investigate the impact of COVID-19 on such low success. After excluding COVID-19 data, the OSRs in the last two time-windows increased to 7.0% & 5.9%. These findings clearly demonstrated the significant negative impacts of the anti-COVID-19 drugs on the success of developing anti-infective drugs. Attention should be paid to the fact that this was an effect of high acceleration of competitive efforts driven by pandemic state of necessity, and the vast majority of trial failures were an outcome of effective vaccines becoming available which made some of the other development efforts redundant or no longer justified by patient need. It was a unique situation that so many were developed in parallel and accelerated to Phase 3 in short time, and thus the effects on overall infectious diseases should be considered separately, which may only affect the short-term trend of anti-infective drugs.

As discovered by previous discussion, the industry-sponsored clinical trials accounted for 70.1% of the trials analyzed in this study, and showed much higher ClinSRs in Fig. 3 comparing with all trials (including the industry-sponsored trials, academic-sponsored trials, and so on). A similar phenomenon was also perceived in Fig. 4b when analyzing the trials for COVID-19 (industry-sponsored trials led to a much higher OSR than all COVID-19 trials). These results indicated that non-industry-sponsored (especially, academic-sponsored) trials gave substantially higher attrition rates than the industry-sponsored ones, which suggested the academic researchers to collaborate with big pharmaceutical company for resources[87]. To realize such collaboration, some strategies were proposed, including (*a*) *resource sharing platform*, in which scientific data, physical entities, professional experiences, etc. from both academia and industry could be openly shared[88]; (*b*) *joint research study*, in which pharmaceutical company either provided financial support for certain project at academic institution or carried out the project jointly with academia[89]; (*c*) *licensing intellectual properties*, in which academic institutions granted pharmaceutical companies the right to develop proprietary technologies[90]; (*d*) *public-private partnership*, in which multiple stakeholders, including pharmaceutical companies, academic institutions, and so on, collaborated on large-scale research endeavors[91]; (*e*) *joint clinical trial*, in which academia and industry cooperated in designing, carrying out and reporting their clinical trials[92].

To overcome the funding limitations and regulatory barriers of academic institutions, the seeking for industry collaboration as discussed above could partially address the challenge[67], however additional actions should be taken. These included the integrations of regulatory science into the educational programs of pharmaceutical professionals[93], the early dialogues with the regulator in translational research plan[94], the proactive communication with regulators throughout drug discovery[95], and the timely attention to translating research findings into clinical practice[96]. Substantial variations in the dynamic ClinSRs among different disease classes were observed in this study (Supplementary Figs. S48–S61), and it was also identified that the success rates for a disease class were not a precise predictor of the success probabilities for individual diseases in that class, which asked for personalized assessments for both disease class and individual disease. Moreover, it was also of great importance to assess the ClinSRs for a drug group of interests. For instance, in the development of anti-COVID-19 drug (as shown in Supplementary Fig. S85c), the ClinSRs of different categories of anti-COVID-19 drugs (such as vaccine, antiviral drug, and immunomodulator) varied greatly, which asked for a measurement for any drug group of interest. Therefore, our online platform *ClinSR.org* was constructed to meet such critical demands.

A clear shift from SMDs to other drug modalities (e.g., antibody-related drug) in current pharmaceutical R&D was observed in Fig. 6, which resulted in a substantial expansion of ARD in clinical trial. Meanwhile, as provided in Supplementary Figs. S62–S65, recent success rates of ARDs greatly surpassed that of other drug modalities, which might originate from its features of exquisite specificity, long serum half-life, high affinity and immune effector function[97]. These features might give guidance for other drug modalities on how to achieve a higher success rate. Moreover, SMDs remained the mainstay of current pharmaceutical R&D, which were key for resolving the problems of *productivity crisis*. Their poor physicochemical properties, unmeaningful efficacy of the chosen target, and constant turmoil of strategy changes with companies should therefore be carefully addressed[68].

Furthermore, the sophisticated factors were identified here and reported by previous publications[29,41,44,50] to contribute to the ClinSRs of drugs. Except for those related to pharmacology, a variety of other invaluable factors might also substantially affect the clinical trial success of drug. (*a*) *Clinical trial design and execution*. For example, due to the heterogeneity of enrolled patients, the trials that could give optimal therapy customization to individuals with specific markers were constructed (such as basket trials and umbrella ones), which had shown that these new trials were ushering in tremendous opportunities for enhancing '*success*'[98]. (*b*) *Special FDA designations for drug development*. For example, the developments of drugs for rare/severe medical condition could be promoted by orphan, fast track, accelerated approval, priority review, and breakthrough therapy which might affect success[31]. (*c*) *Development strategy of pharmaceutical companies*. For example, many pharmaceutical companies had taken advantages of the depth and breadth of the *contract research organizations* (CROs)

and outsourced many of the R&D activities as a way of reducing risks and costs, which was also likely to affect trial successes[99]. (*d*) *ICMJE policy and FDA regulations*. Since the incomplete registrations of trials might inflate resulting ClinSRs, the scope and content expansions of mandatory trial registration by policies would thus make the trial data more and more comprehensive and the calculated ClinSRs more and more accurate.

Additionally, different stakeholders (including pharmaceutical company, investor, and regulatory agency) might benefit from the online platform "*ClinSR.org*". For a pharmaceutical company, the *ClinSR.org* might be useful for benchmarking its R&D project management, resource allocations, and portfolio decision[5]. Particularly, by leveraging the *ClinSR.org*, pharmaceutical companies could assess the success rate of its own clinically-tested drugs, which might aid in optimizing its pipeline decision. For an investor, the *ClinSR.org* might also be applied to guide decision-making when funding the developmental program for therapeutic candidate[4]. Specifically, *ClinSR.org* could be used to measure the probability of clinical trial success for certain type of drug candidate, which might be helpful for enabling prudent resource allocation and adjusting capital investment strategy. For a regulatory agency, *ClinSR.org* could realize a retrospective evaluation of how the currently-implemented policy impacted clinical trial success rates of drug discovery[6]. Notably, *ClinSR.org* performed a longitudinal study (spanning decades since the beginning of this century) of clinical success rates, which might be used to evaluate the effectiveness of formulated policies (like *orphan drug designation*) in promoting innovation or addressing unmet medical needs.

In summary, this study tried to establish a reproducible, robust & reliable protocol which enabled a public data-based assessment of ClinSRs, and may be adopted as a reference by future analyses when assessing ClinSRs. An explicit procedure for data standardization was defined, the in-depth descriptions of which were critical for the reproduction of our study by others; a dynamic strategy for measuring ClinSRs was proposed in this study based on the assessment of method robustness; careful analysis & correction of the inherent bias in the data of *publicly-accessible database* were conducted. Building on these contributions, some interesting findings were also discovered.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

All data used in this study were collected from ClinicalTrials.gov (https://clinicaltrials.gov/), Drugs@FDA (https://www.fda.gov/drugs) and Pharmaprojects (https://citeline.informa.com/). The datasets generated for calculating ClinSR during the current study are available on the online platform *ClinSR.org* (https://ClinSR.org/), which is accessible without login requirement by user. The source data and figures that support the findings of this study are also available in Figshare https://doi.org/10.6084/m9.figshare.29646407) Source data are provided with this paper.

Code availability

Python 3.10 is used for data analysis. All code supporting the analyses is available at *ClinSR.org* (https://ClinSR.org/).

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Author contributions

F.Z. conceived the idea, and designed the entire study; Yi.Z., Y.T.Z., H.W.X., Z.C., S.J.H., Y.H.L., J.B.F, D.H.Z., X.Y.S., and X.C.L. collected the data; Yi.Z., Y.T.Z. and H.N.Z. performed the data analyses; Yi.Z., Y.T.Z., Z.C., S.J.H., Yu.Z., K.X.L., Y.Q.Q., L.Y.H., and H.B.D. generated figures & tables; Yi.Z. and Y.T.Z. designed and constructed the website of *ClinSR.org*; F.Z., Yi.Z., Y.T.Z., H.W.X., Y.Z.W. and W.Q.X. contributed to the revision; F.Z. and Yi.Z. wrote the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to Feng Zhu.

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