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ORIGINAL RESEARCH ARTICLE

Patient Enrollment per Month (Accrual) in Clinical Trials Leading to the FDA Approval of New Cancer Drugs

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Abstract

Background Insufficient patient enrollment per month (=accrual) is the leading cause of cancer trial termination.

Objective To identify and quantify factors associated with patient accrual in trials leading to the US Food and Drug Administration (FDA) approval of new cancer drugs.

Data All anti-cancer drugs with FDA approval were identified in the Drugs@FDA database (2000–2022). Data on drug indication's background-, treatment-, disease-, and trial-related factors were collected from FDA labels, clinicaltrials.gov, and the Global Burden of Disease study. The association between patient accrual and collected variables was assessed in Poisson regression models reporting adjusted rate ratios (aRR).

Results We identified 170 drugs with approval in 455 cancer indications on the basis of 292 randomized and 163 single-arm trials. Among randomized trials, median enrollment per month was 38 patients (interquartile range [IQR]: 26–54) for non-orphan, 21 (IQR: 15–38, aRR 0.88, $p = 0.361$) for common orphan, 20 (IQR: 10–35, aRR 0.73, $p < 0.001$) for rare orphan, and 8 (IQR 6–12, aRR 0.30, $p < 0.001$) for ultra-rare orphan indications. Patient enrollment was positively associated with disease burden [aRR: 1.0003 per disability-adjusted life year (DALY), $p < 0.001$), trial sites (aRR: 1.001 per site, $p < 0.001$), participating countries (aRR: 1.02 per country, $p < 0.001$), and phase 3 vs. 1/2 trials (aRR: 1.64, $p = 0.037$). Enrollment was negatively associated with advanced-line vs. first-line treatments (aRR: 0.81, $p = 0.010$) and monotherapy vs. combination treatments (aRR: 0.80, $p = 0.007$). Patient enrollment per month was similar between indications with and without a biomarker (median: 27 vs. 32, aRR 0.80, $p = 0.117$). Patient enrollment per month was substantially lower in government-sponsored than industry-sponsored trials (median: 14 vs. 32, aRR 0.80, $p = 0.209$). Enrollment was not associated with randomization ratios, crossover, and study blinding.

Conclusions Disease incidence and disease burden alongside the number of study sites and participating countries are the main drivers of patient enrollment in clinical trials. For rare disease trials, greater financial incentives could help expedite patient enrollment. Novel trial design features, including skewed randomization, crossover, or open-label masking, did not entice patient enrollment.

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1 Introduction

Clinical trials are the fundament of evidence-based medicine. Trials inform physicians which treatments improve patient outcomes. Although 70% of US citizens are inclined to participate in trials [1], merely 3–5% of cancer patients are enrolled [2]. As a result, 20–40% of trials close owing to insufficient patient enrollment [3, 4]. Insufficient patient enrollment is the leading cause of early termination in cancer trials [5, 6]. Therefore, there is great clinical and economic interest from academia, governments, and industry to increase trial participation and expedite patient enrollment.

Systematic reviews sought to identify barriers to clinical trial participation [7–16]. These studies found that

Key Points

This study identifies factors associated with the speed of patient enrollment using data from 170 drugs with FDA approval in 455 cancer indications (2000–2022).

Disease incidence, disease burden, the FDA orphan designation, the number of clinical trial sites, and the number of participating countries were the main drivers of fast patient accrual.

Contemporary trial designs believed to entice patient enrollment, e.g., skewed randomization, crossover, or open-label masking, were not associated with faster patient enrollment.

Greater financial incentives leading to more study sites and closer international collaboration could expedite patient enrollment for (ultra-)rare orphan drugs.

eligibility criteria, industry sponsorship, number and location of study sites, underlying cancer diseases, disease burden, disease incidence, trial phase, and the number of enrolled patients may influence patient participation and clinical trial completion. On the basis of these findings, scholars conceptualized that patient enrollment is moderated by a unique mix of background, treatment-related, disease-related, trial design, and patient-related factors [7–9]. However, prior studies examining clinical trial enrollment and patient accrual are often limited in their scope of analyzed clinical trials, analyzed time horizon, examined variables, frequently only examine enrollment barriers at single study sites, and tend to focus on government-sponsored rather than industry-sponsored trials [17–22].

Furthermore, pharmaceutical companies frequently argue that certain clinical trial design features may entice patients to participate in clinical trials. It is believed that the option to crossover from the control to the treatment arm for nonresponders, active comparators, skewed randomization that increases the probability of being allocated to the treatment arm, and open-label blinding encourage patients to enroll in clinical trials [23]. However, the role of these clinical trial design features for patient accrual remains debated [9, 17, 18].

This is the largest cross-sectional study to identify and quantify background, treatment-related, disease-related, and trial design factors that are associated with patient accrual in clinical trials supporting the FDA approval of 170 drugs in 455 anti-cancer indications from 2000 to 2022.

2 Data and Methods

2.1 Sample Identification

All new drug applications and biologic license applications with FDA approval from 1 January 2000 to 1 January 2022 were identified in the Drugs@FDA database. We examined US drug approvals, given that most trials focus on the US and the FDA is typically the first regulatory agency to authorize new drugs [24]. Then, we limited the sample to anti-cancer treatments, excluding non-cancer drugs, supportive cancer agents, diagnostic medicines, and anti-emetics for cancer patients. For these anti-cancer drugs, we then screened the Drugs@FDA database to identify all their original and supplemental indications with FDA approval until 1 January 2022.

2.2 Data Collection

Two independent reviewers collected background-, treatment-, disease-, and trial-related variables from FDA labels, clinicaltrials.gov, associated clinical trial publications, and the Global Burden of Disease study for all identified cancer drugs and supporting clinical trials. The first reviewer (D.T.M.) obtained data from FDA labels, which the second reviewer (T.M.) then cross-checked and extended with data found on clinicaltrials.gov and associated peer-reviewed publications. Full details of the data extraction method have been described elsewhere [25–27].

Patient accrual rate The primary endpoint of this study was the patient accrual rate. The patient accrual rate was calculated by the quotient of the total number of recruited patients and the total enrollment period. The patient accrual rate measures the efficiency of patient recruitment [17, 18]. A high accrual rate indicates very efficient patient recruitment, and vice versa.

Background factors We classified the primary clinical trial sponsor (industry vs. government) and obtained the total number of clinical trial sites and the total number of participating countries to describe background-related factors.

Treatment-related factors Drug indications were characterized by their novelty/innovativeness (first-in-indication vs. advance-in-indication vs. addition-to-indication), mechanism of action (cytotoxic chemotherapy vs. targeted therapies vs. immune regulators), biomarkers status, line of therapy (first-line vs. advanced-line), and treatment type (combination therapy vs. monotherapy). Indication novelty was independently assessed by two medical doctors on the basis of the World Health Organization's Anatomical Therapeutic Chemical code. Adapting Lanthier et al.'s classification of drug innovation and modifying it to indications [28],

we considered drugs that were the first in a class to treat a new disease as "first-in-indication" drugs that were not the first in a class to treat a new disease but approved under FDA priority review as "advance-in-indication" and all others as "addition-to-indication".

Disease-related factors We obtained disability-adjusted life years (DALYs) for the US population in 2019 from the Global Burden of Disease study to describe the burden of each cancer disease [29]. Furthermore, we accessed the FDA's orphan drug database to link the orphan designation status to each indication. Given the existence of distinct orphan subgroups [26], we stratified orphan indications according to the number of affected US inhabitants into common (> 200,000), rare (200,000–6600), and ultra-rare (< 6600).

Trial design Clinical trials were differentiated by their design (randomized vs. single-arm), phase (phase 1/2 vs. phase 3), masking (open-label vs. double-blind), comparator (active vs. placebo/no treatment), randomization (equal vs. skewed), and crossover (not-specified vs. allowed vs. not allowed).

2.3 Statistical analysis

We used descriptive statistics to present the sample's baseline characteristics. We conducted distinct analyses for randomized and single-arm trials given their unique characteristics in trial designs and high collinearity with other variables in the dataset. Frequencies were compared using Fisher's exact test.

First, we conducted a univariable analysis to identify and quantify factors associated with patient accrual. For categorical variables, median accrual rates with interquartile ranges (IQR) were compared using Kruskal–Wallis tests. The association between interval-scaled variables and accrual rates was explored in a univariable regression analysis. The patient accrual rate was specified as the dependent variable.

Thereafter, we conducted a multivariable regression analysis. All collected variables were included in the analysis, except for those identified as collinear in a Pearson correlation matrix, e.g., disease type and orphan designation (Table e1). For the regression analyses, we used Poisson models to account for the left-skewed distribution of the patient accrual rate. For the Poisson regression analysis, we report adjusted rate ratios (aRR) with 95% confidence intervals (95% CI). All regression models account for molecule-clustered standard errors. Furthermore, we conducted an alternative regression model including the FDA approval type (standard approval vs. accelerated approval) as an independent variable.

Data were stored in Microsoft Excel (Microsoft Corp) and analyzed with Stata software, version 14.2 (StataCorp LLC). Two-tailed *p*-values below 0.05 were considered significant.

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines where applicable.

3 Results

3.1 Sample Overview

A total of 720 new drugs were granted FDA approval from 2000 to 2022. Of these, 170 drugs were approved for anticancer treatment with a total of 455 FDA-approved indications (Fig. 1).

Of these 455 indications, 292 (64%) were supported by randomized trials and 163 (36%) by single-arm trials. A median of 330 patients (IQR: 128–676) were enrolled per clinical trial with a median accrual rate of 18 patients per month (IQR: 7–36). The majority of trials were sponsored by the pharmaceutical industry (428, 94%). Trials were conducted at a median of 92 sites (IQR: 38–151) across 15 countries (IQR: 8–22). Industry-sponsored trials were conducted at significantly more sites (97 vs. 43, $p = 0.034$) and countries (16 vs. 2, $p < 0.001$) than government sponsored trials (Table e2). New drug indications were innovative with the majority being first-in-indication (176 [39%]) or addition-to-indication (211 [46%]). The mechanism of action was cytotoxic chemotherapy for 32 indications (7%), targeted for 273 indications (60%), and immune regulatory for 150 indications (33%). The FDA approved 167 indications (37%) on the basis of a biomarker. Indications were predominantly advanced-line (238 [52%]) monotherapies (298 [65%]) for solid cancers (301 [66%]). The median DALY rate per 100,000 US inhabitants was 117 (IQR: 31–428). The FDA orphan designation was granted to 294 indications, of which 64 (14%) were for common, 205 (45%) for rare, and 25 (5%) for ultra-rare diseases. Randomized and single-arm trials significantly differed in background, treatment-related, and disease-related variables (Table 1). Among the 292 randomized trials, 176 were open-label (60%), 187 (64%) compared the new drug with placebo or no treatment, and 197 (67%) trials used an equal randomization ratio. Crossover was not specified in 153 trials (52%), allowed in 68 trials (23%), and not permitted in 71 trials (24%).

3.2 Randomized trials

Among randomized trials, patient enrollment per month was significantly faster for industry- than government-sponsored trials (median: 32 vs. 14 patients per month, $p < 0.001$). In the univariable analysis, the patient accrual rate was significantly correlated with the total number of trial sites (Fig. 2a) and countries (Fig. 2b). Slower patient enrollment

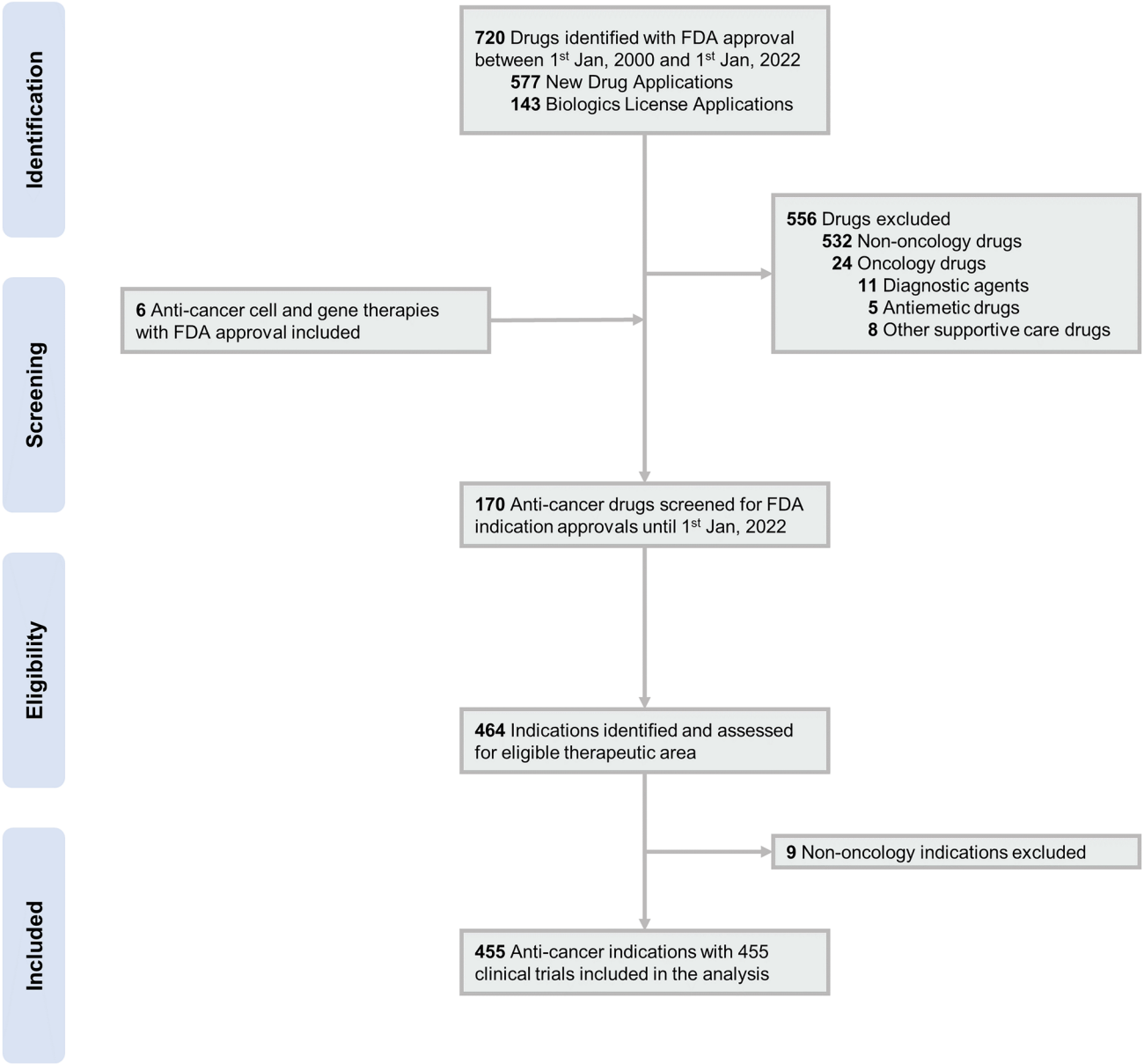

Fig. 1 New cancer drugs and clinical trials included in the analysis. *CAR* chimeric antigen receptor, *FDA* US Food and Drug Administration

per month was observed for more innovative indications. Drug indications considered that first-in-indication enrolled fewer patients per month than those considered advance-in-indication and addition-to-indication (median: 22 vs. 33 vs. 32 patients per month, p =0 .005). Accrual was slower for monotherapies than combination treatments (median: 23 vs. 36, $p < 0.001$). Patient accrual was substantially slower for hematologic than solid cancer trials (median: 15 vs. 33, $p < 0.001$) and orphan than non-orphan cancer trials (median: 20 vs. 38, $p < 0.001$). Particularly fewer patients were enrolled in clinical trials for ultra-rare orphans relative to rare, common, and non-orphan cancers (median: 8 vs. 20 vs. 21 vs. 38 patients per month, $p < 0.001$). Accordingly, accrual rates were significantly associated with the burden of disease measured by DALYs (Fig. 2c). Slower patient enrollment was furthermore observed among phase 1/2 than phase 3 trials (median: 9 vs. 33, $p < 0.001$) and open-label than double-blind trials (median: 26 vs. 34, $p = 0.024$). No significant difference in the number of patients enrolled per month was observed for trials with an active comparator, skewed randomization, or trials that allowed cross-over to the new drug.

Table 1 Sample overview

No. (%)	Randomized	Single-arm	*p* value[a]	Total
No. of enrolled patients	567 (319-807)	106 (79 -156)	<0.001	330 (128–676)
Patient accrual per month	31 (15-44)	6 (3-13)	<0.001	18 (7-36)
Background-related factors				
Primary trial sponsor			0.839	
Industry	274 (94)	154 (94)		428 (94)
Government	18 (6)	9 (6)		27 (6)
No. of trial sites	128 (82–175)	34 (21–56)		92 (38–151)
No. of trial countries	19 (13–25)	8 (2–11)		15 (8–22)
Treatment-related factors				
Indication innovativeness[b]			<0.001	
Addition-to-indication	51 (17)	17 (10)		68 (15)
Advance-in-indication	156 (53)	55 (34)		211 (46)
First-in-indication	85 (29)	91 (56)		176 (39)
Mechanism of action			0.154	
Cytotoxic chemotherapy	21 (7)	11 (7)		32 (7)
Targeted therapies	184 (63)	89 (55)		273 (60)
Immune regulators	87 (30)	63 (39)		150 (33)
Biomarker			0.311	
No	190 (65)	98 (60)		288 (63)
Yes	102 (35)	65 (40)		167 (37)
Line of therapy			<0.001	
First-line	177 (61)	40 (25)		217 (48)
Advanced-line	115 (39)	123 (75)		238 (52)
Treatment type			<0.001	
Combination therapy	141 (48)	16 (10)		157 (35)
Monotherapy	151 (52)	147 (90)		298 (65)
Disease-related factors				
Cancer disease			<0.001	
Hematologic	68 (23)	86 (53)		154 (34)
Solid	224 (77)	77 (47)		301 (66)
DALYs[c]	132 (94–428)	45 (15–117)		117 (31–428)
FDA Orphan Designation			<0.001	
Non-orphan	127 (43)	34 (21)		161 (35)
Orphan	165 (57)	129 (79)		294 (65)
Reformed Orphan Designation[d]			<0.001	
Non-orphan	127 (43)	34 (21)		161 (35)
Common orphan	46 (16)	18 (11)		64 (14)
Rare orphan	115 (39)	90 (55)		205 (45)
Ultra-rare orphan	4 (1)	21 (13)		25 (5)
Trial-related factors				
Phase			<0.001	
Phase 1/2	34 (12)	155 (95)		189 (42)
Phase 3	258 (88)	8 (5)		266 (58)
Masking				
Open-label	176 (60)	NA		NA
Double blind	116 (40)	NA		NA
Comparator				
Active	105 (36)	NA		NA

Table 1 (continued)

No. (%)	Randomized	Single-arm	*p* value[a]	Total
Placebo/no treatment	187 (64)	NA		NA
Randomization[e]				
Equal	197 (67)	NA		NA
Skewed	74 (25)	NA		NA
Crossover				
Not specified	153 (52)	NA		NA
Allowed	68 (23)	NA		NA
Not allowed	71 (24)	NA		NA
Total	292 (100)	163 (100)		455 (100)

DALYs disability-adjusted life years, *FDA* US Food and Drug Administration, *NA* not applicable

[a]*P* values are based on Kruskal–Wallis tests and Fisher's exact tests

[b]Drugs that were the first to treat a new disease were considered as "first-in-indication" drugs that were not the first to treat a new disease but approved under FDA priority review as "advance-in-indication" and all others as "addition-to-indication"

[c]DALYs as rate per 100,000 US inhabitants

[d]Orphan indications were further stratified according to the number of affected US inhabitants into common (> 200,000), rare (200,000–6600), and ultra-rare (< 6600).

[e]Skewed randomization refers to unequal patient randomization ratios, e.g., 2:1, 3:1, 3:2, 2:1:1

Results of the multivariable Poisson regression for randomized trials are presented in the second column of Table 2. Patient enrollment was slower, yet not significant at a 5% level owing to the high collinearity between the number of study sites and countries, for government- than industry-sponsored trials (aRR: 0.80, 95%CI 0.56–1.13, $p = 0.209$). The accrual rate was significantly associated with the number of trial sites (aRR: 1.001, 95%CI 1.001–1.002, $p < 0.001$) and the number of participating countries (aRR: 1.02, 95%CI 1.01–1.03, $p < 0.001$). Patient accrual was negatively associated with advanced-line relative to first-line treatment (aRR: 0.81, 95%CI 0.69–0.95, $p = 0.010$), monotherapy relative to combination treatments (aRR: 0.80, 95%CI 0.69–0.94, $p = 0.007$). Patient enrollment was substantially faster in phase 3 than in phase 1 or 2 trials (aRR: 1.64, 95%CI 1.03–2.62, $p = 0.037$). Patient enrollment was slower for ultra-rare (aRR: 0.30, 95%CI 0.24–0.38, $p < 0.001$), rare (aRR: 0.73, 95%CI 0.61–0.88, $p < 0.001$), and common (aRR: 0.88, 95%CI 0.68–1.15, $p = 0.361$) orphan than non-orphan cancers. Accrual was not associated with trial blinding, crossover, comparator, randomization ratio, mechanism of action, and biomarker status. The alternative regression model shows that accelerated approval was not significantly associated with the accrual rate (Table e3).

3.3 Single-arm trials

In the univariable analysis, faster patient enrollment was observed for industry- than government-sponsored trials (median: 6 vs. 3 patients per month, $p = 0.031$) (Table 3). However, this association was not significant after adjusting for further variables (aRR: 0.65, 95%CI 0.26–1.64, $p = 0.366$). In the multivariable model, the number of study sites was positively correlated to accrual rates (aRR: 1.007, 95%CI 1.003–1.012, $p = 0.003$). Patient enrollment per month was substantially slower for trials in the advanced-line than the first-line setting (aRR: 1.42, 95%CI 1.01–2.00, $p = 0.042$). Relative to cytotoxic chemotherapy, patient accrual was faster in trials for immune-regulating drugs (aRR 2.35, 95%CI 1.24–4.48, $p = 0.009$). Relative to non-orphan drugs, trials evaluating new ultra-rare orphan drugs were associated with slower patient accrual (aRR 0.58, 95%CI 0.38–0.90, $p = 0.015$). In the alternative regression models accelerated approval was not significantly associated with the accrual rate (Table e4).

4 Discussion

This cross-sectional study analyzed factors associated with clinical trial enrollment on the basis of a sample of 170 drugs with FDA approval across 455 cancer indications. We found that several background-, treatment-, and disease-related factors significantly influence the speed of patient enrollment (e.g., the patient accrual rate). Patient accrual is predominantly influenced by the number of participating study sites and countries and the underlying disease incidence and burden (orphan designation status), rather than clinical trial design features.

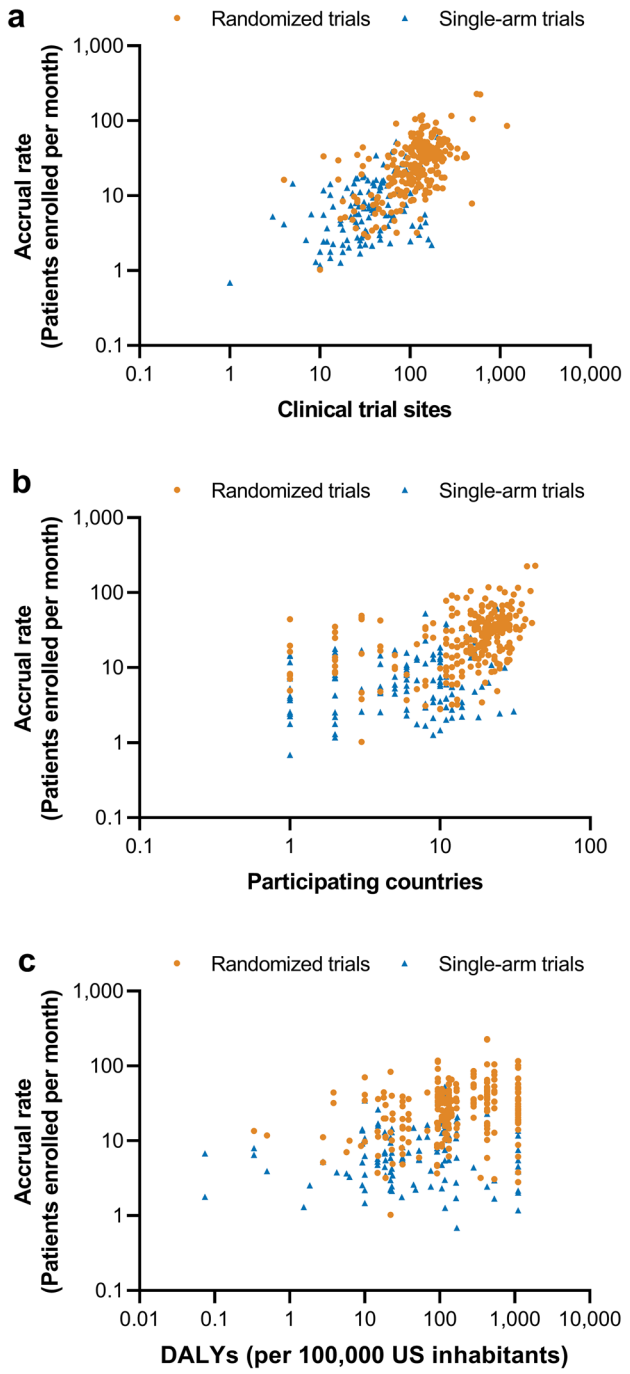

Fig. 2 Association between patient enrollment per month and study sites, participating countries, and DALYs in cancer trials. **a** Illustrates the association between patient accrual rates and the total number of registered trial sites; **b** portrays the association between patient accrual rates and the total number of participating countries; **c** visualizes the association between patient accrual rates and DALYs (as a rate per 100,000 US inhabitants). The accrual rate, number of registered trial sites, number of participating countries, and DALYs are illustrated on the graphs *y* and *x* axis on a logarithmic scale. *DALYs* disability-adjusted life years, *FDA* US Food and Drug Administration

4.1 Background Factors

Consistent with previous literature [9, 10, 17, 20, 22], this study finds that patient enrollment per month was positively associated with the total number of study sites and participating countries as well as industry sponsorship, especially for randomized trials. These findings indicate that patient enrollment leading to successful trial completion is mainly driven by the financial funding and existing administrative structure to conduct these trials. Of note, industry-sponsorship was not significantly associated with patient accrual, likely owing to collinearity between industry-sponsorship with the number of study sites and participating countries. Pharmaceutical corporations that partner with clinical research organizations and academic and non-academic study sites will, of course, find more eligible patients in a shorter timeframe than government-sponsored clinical trial networks with limited funding that seek to enroll patients at a few study sites in a single country.

In this study, pivotal clinical trials in oncology were conducted at a median of 15 countries globally. However, prior research showed that trials predominantly enrolled patients from high-income countries with only few trials (29%) enrolling patients in low-income countries [30]. Increasing trial participation in low-income countries could expedite patient accrual, allow for faster patient access to new medicines, and test new drugs in a more diverse patient population [31].

4.2 Treatment-Related Factors

Results indicate that the line of therapy, therapy type, and the drug indication's innovativeness were significantly associated with patient enrollment per month. Similar to prior studies [9, 17], faster patient enrollment was observed in trials for first-line than advanced-line treatments. There is simply a larger eligible patient population that can participate in first-line than advanced-line trials. Furthermore, very innovative drugs are often first tested as monotherapy in advanced-line treatments for common diseases and then "move up" the therapeutic ladder to first-line combination therapies if they continue to show clinical benefit relative to the standard of care [25]. Further, pharmaceutical companies were shown to be inclined to first test and seek approval for cancer drugs with multiple indications in rare diseases such that they receive the orphan designation's benefits [32]. This commercialization strategy is also referred to as "orphan-first"[33]. These factors could explain the lower patient accrual rates observed for first-in-indication drugs.

Table 2 Patient accrual per month in randomized cancer trials

	Univariable			Multivariable Poisson regression		
	Median	IQR	*p* value	Adjusted rate ratio	(95% CI)	*p* value
Background-related factors						
Trial sponsor						
Industry	32	(16–44)		1	Reference	
Government	14	(8–25)	0.001	0.80	(0.56–1.13)	0.209
No. of trial sites[a]	1.002	(1.001–1.003)	0.000	1.001	(1.001–1.002)	0.000
No. of trial countries[a]	1.04	(1.03–1.06)	0.000	1.02	(1.01–1.03)	0.000
Treatment-related factors						
Indication innovativeness[b]						
Addition-to-indication	32	(17–61)		1	Reference	
Advance-in-indication	33	(18–44)		0.84	(0.7–1.01)	0.071
First-in-indication	22	(10–38)	0.005	0.79	(0.63–0.98)	0.035
Mechanism of action						
Cytotoxic chemotherapy	21	(9–37)		1	Reference	
Targeted therapies	30	(15–42)		0.98	(0.73–1.31)	0.867
Immune regulators	34	(17–47)	0.148	1.06	(0.79–1.43)	0.691
Biomarker						
No	32	(15–44)		1	Reference	
Yes	27	(16–44)	0.842	0.88	(0.76–1.03)	0.117
Line of therapy						
First-line	33	(17–45)		1	Reference	
Advanced-line	25	(13–38)		0.81	(0.69–0.95)	0.010
Treatment type						
Combination therapy	36	(19–45)		1	Reference	
Monotherapy	23	(13–36)	0.001	0.80	(0.69–0.94)	0.007
Disease-related factors						
Cancer disease						
Hematologic	15	(9–35)				
Solid	33	(19–46)	0.000			
DALYs[a,c]	1.0003	(1.0002–1.0005)	0.000			
FDA Orphan Designation						
Non-orphan	38	(26–53)				
Orphan	20	(11–36)	0.000			
Reformed Orphan Designation[d]						
Non-orphan	38	(26–53)		1	Reference	
Common orphan	21	(15–38)		0.88	(0.68–1.15)	0.361
Rare orphan	20	(10–35)		0.73	(0.61–0.88)	0.001
Ultra-rare orphan	8	(6–12)	0.000	0.30	(0.24–0.38)	0.000
Trial-related factors						
Phase						
Phase 1/2	9	(4–16)		1	Reference	
Phase 3	33	(19–44)	0.000	1.64	(1.03–2.62)	0.037
Masking						
Open-label	26	(13–42)		1	Reference	
Double blind	34	(19–44)	0.024	1.07	(0.82–1.39)	0.627
Comparator						
Active	33	(18–44)		1	Reference	
Placebo/no treatment	29	(15–42)	0.284	0.96	(0.73–1.27)	0.799

Table 2 (continued)

	Univariable			Multivariable Poisson regression		
	Median	IQR	*p* value	Adjusted rate ratio	(95% CI)	*p* value
Randomization[e]						
Equal	33	(16–44)		1	Reference	
Skewed	26	(16–40)	0.186	0.96	(0.8–1.15)	0.647
Crossover						
Not specified	30	(14–41)		1	Reference	
Allowed	25	(15–42)		1.13	(0.97–1.33)	0.125
Not allowed	34	(18–49)	0.092	1.13	(0.97–1.32)	0.124

DALYs disability-adjusted life years, *FDA* US Food and Drug Administration

[a]For interval-scaled variables, Poisson correlation coefficients are presented in the univariable column

[b]Drugs that were the first to treat a new disease were considered as "first-in-indication" drugs that were not the first to treat a new disease but approved under FDA priority review as "advance-in-indication" and all others as "addition-to-indication"

[c]DALYs as rate per 100,000 US inhabitants

[d]Orphan indications were further stratified according to the number of affected US inhabitants into common (> 200,000), rare (200,000–6600), and ultra-rare (< 6600)

[e]Skewed randomization refers to unequal patient randomization ratios, e.g., 2:1, 3:1, 3:2, 2:1:1

4.3 Disease-Related Factors

Consistent with prior studies [9, 10, 17, 20, 22], our findings show that patient enrollment per month is influenced by disease incidence and burden. Patient accrual was particularly low for orphan drugs (median enrollment per month: 20 vs. 38 patients), which are defined as drugs for diseases with a prevalence below 200,000 US inhabitants, or drugs with limited sales potential. However, there are certain orphan subgroups with different disease dynamics [26]. Regarding these orphan subgroups, our results underline patient enrollment in clinical trials significantly differs. Results indicate that patient accrual is substantially more complex for ultra-rare diseases, defined by a prevalence threshold below 6600 US inhabitants equating to 1 in 50,000, than rare or non-orphan drugs (median enrollment per month: 8 vs. 20 vs. 38 patients). Meanwhile, there was no significant difference between common orphan drugs that received the FDA orphan designation albeit their disease prevalence is beyond 200,000 US inhabitants, and non-orphan drugs (median enrollment per month: 21 vs. 38 patients, aRR 0.88, $p = 0.361$). These common orphan drugs are often targeted or immune therapies treating biomarker-defined subsets of common diseases [26].

Conducting clinical trials and developing drugs for rare diseases has emerged as "an economically viable strategy" owing to greater financial incentives, lower trial failure rates, and higher drug prices resulting in greater firm valuations and returns for pharmaceutical companies [34, 35]. Although a the share of newly developed orphan drugs has surged over the past decades, orphan drug development has concentrated on few diseases [36]. FDA-approved drugs exist for merely 5% of the more than 7000 rare diseases [36]. Further, clinical trials with new drugs are currently under development only for 15% of these more than 7000 rare diseases [36]. As a result many patients continue to suffer from rare diseases without treatment options—particularly those with ultra-rare diseases. The main challenge in conducting trials for ultra-rare diseases is finding competent investigators that recruit a sufficient number of patients at study sites with an adequate technological infrastructure. These challenges could be overcome by increasing funding for ultra-rare diseases, such that there are more financial resources available to pay clinical specialists that see patients with ultra-rare diseases regularly and provide the highly complex biotechnological infrastructure that is often necessary to administer new treatments for ultra-rare diseases (e.g., gene and cell therapies) across multiple countries. As previously highlighted, increasing the total number of participating study sites and countries will likely also increase patient accrual. Therefore, ultra-rare disease trials must be conducted as an international endeavor across nations where pharmaceutical companies closely collaborate with national healthcare providers and patient organizations in each region. Furthermore, decentralized clinical trials (DCTs) could help to enroll the very limited and geographically disperse patient population that defines these N-of-1 (ultra-rare) diseases [37]. With DCTs, patients are not bound to a single study site, which often demands lengthy travel, in a country to participate in clinical trials for their disease, but could effortlessly enroll in trials with the help of telehealth infrastructure, online consent

Table 3 Patient accrual per month in single-arm cancer trials

	Univariable			Multivariable Poisson regression		
	Median	IQR	*p* value	Adjusted Rate Ratio	(95% CI)	*p* value
Background factors						
Trial sponsor						
Industry	6	(3–14)		1	Reference	
Government	3	(2–7)	0.031	0.65	(0.26–1.64)	0.366
No. of trial sites [a]	1.007	(1.002–1.012)	0.008	1.007	(1.003–1.012)	0.003
No. of trial countries [a]	1.04	(0.99–1.08)	0.096	0.999	(0.969–1.03)	0.955
Treatment-related factors						
Indication innovativeness [b]						
Addition-to-indication	10	(3–14)		1	Reference	
Advance-in-indication	6	(4–15)		1.42	(0.95–2.12)	0.087
First-in-indication	6	(3–11)	0.883	1.09	(0.7–1.69)	0.707
Mechanism of action						
Cytotoxic chemotherapy	3	(2–6)		1	Reference	
Targeted therapies	6	(3–11)		1.63	(0.84–3.16)	0.150
Immune regulators	7	(4–16)	0.060	2.35	(1.24–4.48)	0.009
Biomarker						
No	7	(4–14)		1	Reference	
Yes	5	(3–10)	0.077	0.78	(0.47–1.3)	0.347
Line of therapy						
First-line	4	(3–6)		1	Reference	
Advanced-line	7	(4–15)		1.42	(1.01–2)	0.042
Treatment type						
Combination therapy	3	(2–7)		1	Reference	
Monotherapy	6	(4–14)	0.089	1.36	(0.85–2.16)	0.201
Disease-related factors						
Cancer disease						
Hematologic	6	(4–10)				
Solid	6	(3–15)	0.565			
DALYs [a,c]	1.0002	(0.9996–1.0008)	0.465			
FDA Orphan Designation						
Non-orphan	8	(4–16)				
Orphan	6	(3–11)	0.030			
Reformed Orphan Designation [d]						
Non-orphan	8	(4–16)		1	Reference	
Common orphan	5	(3–6)		0.79	(0.47–1.32)	0.373
Rare orphan	6	(3–12)		0.75	(0.53–1.07)	0.117
Ultra-rare orphan	6	(4–9)	0.158	0.58	(0.38–0.9)	0.015
Trial design						
Phase						
Phase 1/2	6	(3–13)		1	Reference	
Phase 3	5	(2–15)	0.848	1.21	(0.72–2.06)	0.473

[a]For interval-scaled variables, Poisson correlation coefficients are presented in the univariable column

[b]Drugs that were the first to treat a new disease were considered as "first-in-indication." drugs that were not the first to treat a new disease but approved under FDA priority review as "advance-in-indication" and all others as "addition-to-indication"

[c]DALYs as rate per 100,000 US inhabitants

[d]Orphan indications were further stratified according to the number of affected US inhabitants into common (> 200,000), rare (200,000–6600), and ultra-rare (< 6600)

forms, mail pharmacies, and electronic patient reported outcomes (ePRO) platforms.

4.4 Trial Design

Apart from the clinical trial phase, trial design features were not associated with faster patient accrual. These findings are consistent with previous studies [9, 17, 18]. A study of 747 trials supported by the National Clinical Trials Network found that trial blinding and comparator were not associated with patient accrual [9]. A study of 69 pivotal FDA approval trials for metastatic solid tumors (2006–2017) found no difference in patient accrual rates for trials with and without crossover [18]. Accordingly, a study of 194 pivotal FDA approval trials for solid and hematologic cancers could not find any association between patient accrual rates and crossover, trial blinding, primary endpoint, and randomization [17]. Although pharmaceutical companies and researchers believe that these clinical trial design features encourage patients to enroll in clinical trials [23], to date no evidence supports this optimistic belief. The use of crossover in clinical trials remains debated. "Although crossover is essential for studies that test the timing or sequence of therapies, […] crossover confounds interpretation of overall survival" [18]. For trials permitting crossover, pharmaceutical companies are frequently using crossover as the main reason why a surrogate endpoint, such as progression-free survival or tumor response, yet not the clinical endpoint, e.g., overall survival, showed a significant result [38]. Scholars increasingly argue in favor of clinical endpoints, e.g., overall survival and quality of life. These patient-centered outcomes are only rarely assessed and reported by cancer trials [39]. However, there is no evidence these endpoints are associated with faster patient enrollment [17], likely given that endpoints are only rarely discussed with and understood by patients [40]. In theory, a skewed randomization ratio favorably increases patients' likelihood to be allocated to the treatment arm (e.g., 2:1, 3:2, 3:1) and should thereby entice enrollment. In practice, there is no evidence that skewed randomization ratios encourage patients to enroll in clinical trials. Perhaps the positive effect of the favorable randomization ratio on patient accrual is alleviated by the greater number of patients required to conduct trials with skewed randomization.

4.5 Limitations

There are certain limitations underlying our analysis. First, we only evaluated clinical trials that lead to the FDA approval of new cancer drugs. Thereby, our sample is biased to only successful trials with sufficient patient accrual. However, Jenei et al. showed that patient accrual results and their interpretation are consistent between successful FDA approval trials and other cancer trials [17]. Furthermore, with this uniquely large dataset of predominantly industry-sponsored trials, our study extends the existing body of research examining barriers to patient accrual in government-sponsored trials. Future research could examine factors associated with completed relative to withdrawn/terminated clinical trials. Second, our analysis focused on trial-level factors affecting patient accrual. However, previous studies highlighted that there are multiple patient-level factors, including socio-economic status, geographic location, age, sex, race, attending physician, and others, that influence patients' decision to enroll in clinical trials [2, 7, 12–14, 16]. Finally, results and policy implications derived from our sample of cancer trials should be confirmed for other therapeutic areas.

5 Conclusions

Insufficient patient enrollment remains the leading cause of early trial termination. Prior studies highlighted patient and physician barriers to clinical trial participation. On the basis of a uniquely large dataset of 170 drugs with FDA approval in 455 cancer indications, we examined trial-level factors associated with patient enrollment per month. In this study, disease incidence and disease burden alongside the number of study sites and participating countries were the main drivers of patient enrollment. More financial incentives for rare disease trials and closer international collaborations could expedite drug development and encourage patient enrollment for (ultra-)orphan drugs. There is no evidence that trial designs that are commonly believed to entice patient enrollment, including skewed randomization, crossover, or open-label masking, result in faster accrual.

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Declarations

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Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent to Participate Not applicable.

Data Sharing Statement All data used in this study were in the public domain. All data relevant to the study are included in the article or uploaded as supplementary information.

Code Availability Not applicable.

Author Contributions D.T.M. and T.M. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. D.T.M. developed the study concept and design, drafted the manuscript, performed statistical analyses, and supervised the study. All authors carried out acquisition, analysis, or interpretation of data, critically revised the manuscript for important intellectual content, and provided administrative, technical, or material support.

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