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What drives cancer clinical trial accrual? An empirical analysis of studies leading to FDA authorisation (2015–2020)

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ABSTRACT

Objective To examine factors associated with accrual rate in industry sponsored clinical trials supporting US Food and Drug Administration (FDA) cancer drug approvals from 2015 to 2020.

Design, setting and participants Retrospective cross-sectional study included 194 pivotal trials supporting cancer drug approvals by the US FDA from 2015 to 2020.

Interventions Clinical trials were analysed for the type of blinding, primary endpoint, whether crossover was specified in the publication, study phase, line of therapy, response rate, investigational sites, manufacturer and randomisation ratio.

Main outcome measures The main outcome was the rate of accrual, which is the number of patients accrued in the study per open month of enrolment.

Results The study consisted of 133 randomised (68%) and 61 (32%) non-randomised clinical trials. In randomised studies, we found the accrual rate was higher in trials investigating first and second line drugs (adjusted rate ratios (aRR): 1.55, 95% CI 1.18 to 2.09), phase III trials (aRR: 2.13, 95% CI 1.48 to 2.99), and for studies sponsored by Merck (aRR: 1.47, 95% CI 1.18 to 2.37), adjusting for other covariates. In contrast, the primary endpoint of a study, presence of crossover, single agent response rate, the number of investigational sites, population disease burden and skewed randomisation ratios were not associated with the rate of accrual. In the non-randomised adjusted model, the accrual rate was 2.03 higher (95% CI 1.10 to 3.92) for clinical trials sponsored by manufacturer, specifically Merck. Primary endpoint, crossover, trial phase, response rate, the number of investigational sites, disease burden or line of therapy were not associated with the rate of accrual.

Conclusion In this cross-sectional study, line of therapy, study phase and manufacturer were the only factors associated with accrual rate. These findings suggest many proffered factors for speedy trial accrual are not associated with greater enrolment rates.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We examine study characteristics associated with accrual rate in studies leading to Food and Drug Administration (FDA) approval.
⇒ We use the endpoint of 'accrual rate' which examines participants enrolled per month, a fraction that denotes the speed of enrolment.
⇒ We are limited by a sample of industry-sponsored registration clinical trials that have successfully accrued patients and reached positive results.
⇒ We are limited to the information provided by publications associated with the FDA approval.
⇒ Two distinct datasets were used to validate our findings and increase the confidence in our results.

INTRODUCTION

Clinical trials are important to inform clinical practice and improve outcomes for patient with cancer. Yet, only 2%–8% of patients enrol in oncology trials.[1 2] Without sufficient accrual, studies may not have enough statistical power to find meaningful results. When studies cannot accrue, they may fail to complete which wastes scarce economic and human resources. The most common reason for a trial to close prematurely is poor accrual.[3] It is estimated 20%–40% of trials investigating new cancer medicines close due to inadequate participant accrual.[3–7]

Given the challenge of participant recruitment in clinical trials, several studies have highlighted barriers to participation.[2 5 6 8 9] Recent literature suggests certain design features as eligibility criteria, randomisation, trial phase, study type, line of therapy, sample size, treatment type and incidence of disease impact may impact study accrual and ultimately completion of oncology trials.[6] As such, methods to improve recruitment to clinical trials is gaining interest.[10]

Prior work has developed models to identify predictors of accrual in varying settings with mixed results.[10–12] For example, Bennette *et al* evaluated 787 cooperative group adult oncology clinical trials between 2000 and 2011 and found phase III studies, trials testing radiotherapy or targeted agents, were associated with low accrual.[11] Tate and Cranmer developed, and validated a predictive model for clinical trial accrual at a single National Cancer Institute and found disease, fewer

number of national sites, presence of a local Institutional Review Board use, longer accrual time and national enrolment goal were independently associated with participant accrual.[10]

While earlier literature has identified several trial-level variables that impact participant accrual, most studies have examined factors associated with low accrual[5 11] with trials from a single institution.[10 11] To date, no study has explored industry-sponsored trials, which are the predominant basis for new drug marketing authorisations. Here, we focus on registration trials, aiming to determine which factors are associated with accrual rate (number of accrued patients per month of enrolment). Studies that accrue at higher rates might have features that entice participants to enrol. Therefore, understanding these characteristics of accrual rate might be important. To that end, we examined the commonality of a malignancy (disease burden), availability to crossover between study arms, open-label (vs blinded) design, the number of trial sites, the ratio of randomisation (1:1 vs 1:2 or beyond) and single agent drug activity (ie, response rate). However, the effect of these factors on accrual rate is unknown. To explore factors associated with accrual rate with a cohort of clinical trials that have successfully accrued patients, we performed an analysis with a cross-section of recent clinical trials underpinning US Food and Drug Administration (FDA) cancer drug approvals from 2015 to 2020.

METHODS

Study design

We conducted a cross-sectional study of anticancer drugs approved by the FDA from January 2015 to December 2020. The search was performed in July 2021. The study examined publicly available data and therefore was exempt from institutional review board approval, in accordance with the US Department of Health and Human Services, 45 CFR §46.102(f). We adhered to the Strengthening the Reporting of Observational studies in Epidemiology reporting guidelines.

Dataset

A systematic search of the FDA Oncology and Hematologic Malignancies Approvals website[13] was completed to identify industry-sponsored clinical trials underpinning cancer drug approvals between January 2015 and December 2020. In oncology, the design and conduct of clinical trials are evolving. The rationale for this study period was to explore characteristics associated with accrual in the most recent trials leading to FDA approval. Supportive care medicines, paediatric indications, biosimilars and drugs tested in the adjuvant setting were excluded. We searched for the publication supporting each drug approval using the National Clinical Trial number. Publications listed on ClinicalTrials.Gov or FDA approvals were included. The name of the drug approved, date and year of approval, indication, tumour type, manufacturer, sample size, enrolment (months), randomisation ratio, tumour type, type of blinding, primary endpoint, number of investigational sites, whether crossover was specified, line of therapy and trial phase were extracted from the publications.

Variables

The outcome variable for our analysis was the accrual rate, calculated by dividing the number of participants accrued in the study by the number of months of enrolment. We used this measure as it denotes efficiency of participant recruitment and is consistent with prior attempts to study accrual.[14] We build on a previous systematic review for trial-level factors affecting accrual and completion of oncology clinical trials.[6] Further variables were added through expertise of the study team. The first explanatory variable was 'primary endpoint'. In the case that there were two primary endpoints, the more rigorous measure was recorded (ie, if progression-free survival (PFS) and overall survival (OS) were listed as coprimary endpoints, OS was recorded). The second covariate was manufacturer. We chose to categorise Pfizer, Roche, Novartis and Merck as separate variables as these companies receive high proportions of revenue from cancer medicines.[15] All other manufacturers were categories as 'other'. The third covariate was 'disease burden'. This covariate was characterised by the total number of deaths per year for each tumour type using 2020 data from the Surveillance, Epidemiology and End Results (SEER) programme.[16] The method of using SEER data as a surrogate for eligible population has been used in other studies.[11 17] Other model covariates included were the number of investigational trial sites, randomisation ratio (skewed or equal), line of therapy (first or second lines, or three and more lines), phase of study (phase I/II or phase III), type of blinding (blinded or not blinded) and single agent response rate.

Statistical methodology

Summary statistics, including the frequency, median and IQR, were computed for each explanatory variable. We compared trial characteristics with median accrual rate using the Wilcoxon signed-rank and χ^2 test. We calculated these measures for the entire dataset of trials and for each analysis cohort (randomised and non-randomised). The outcome variable of accrual was highly left-skewed rate data which needed a Poisson regression model to account for the non-normal distribution.

We estimated two Poisson regression models using the dependant variable of accrual rate—the first model with randomised studies and the second model with non-randomised studies. To correct for over-dispersion, we fit a model using a negative binomial. The choice to stratify our analysis by randomisation was made because certain variables were deemed to be collinear or interaction terms when analysed as one cohort (ie, randomisation, blinding, randomisation ratio, trial phase and crossover in the non-randomised cohort). We adjusted each of the two models—blinding, primary endpoint, disease burden, line of therapy, crossover, randomisation, trial

phase, single agent response rate, investigational sites and manufacturer. We used Akaike information criterion model selection to distinguish among a set of possible models describing the relationship between accrual rate and trial characteristics. The best-fit model was selected. Adjusted rate ratios were reported with 95% CIs. Statistical significance was set at α=0.05, and tests were two-tailed. Data collection and analyses were performed from August to 10 December 2021. We conducted all analyses using R software, V.3.6.2.

Secondary analysis

To confirm the validity of our findings, we conducted an additional analysis in a separate dataset with a convenience sample of 146 RCTs published in the top six journals from 2018 to 2020. RCTs were selected from *The New England of Medicine*, *The Lancet*, *JAMA*, *The Lancet Oncology*, *Journal of Clinical Oncology* and *JAMA Oncology*, per impact-factor scores on Scimago Journal and Country Rank and that published human randomised trials. We included randomised studies investigating anticancer medicines in the advanced or metastatic setting (surgical and radiotherapeutic studies were excluded). Studies were excluded if they did not evaluate anticancer medicines, such as supportive measures, or were research letters, as they did not provide adequate information for data extraction. Data extraction and statistical analysis were applied using the same methods as the primary analysis.

Patient and public involvement

No patients or public involved.

RESULTS

Table 1 reports the descriptive characteristics and accrual rate of 194 oncology clinical trials included in our study. The study consisted of 133 randomised (68%) and 61 (32%) non-randomised clinical trials. The median sample size was 371 participants (IQR: 210–437) and enrolment 22 months (IQR: 16–31). Of the 194 clinical trials, 162 (84%) tested medicines in the first or second line, whereas 32 (16%) investigated drugs in third line and beyond. Most of the studies used single blinding or less (162 (84%); p<0.001), used an equal randomisation ratio (95 (49%); p<0.001) and did not specify crossover (138 (71%); p<0.001).

Randomised studies enrolled more patients (median sample (IQR), 466 (319–669)) compared with non-randomised studies (105 (74–206)) (table 2). The median months for participant accrual into the study was 22 months for randomised (IQR: 16–27) and 22 months non-randomised (IQR: 74–206) studies. However, accrual rate differed between study cohorts (randomised (IQR): 22 (15–36); non-randomised: 5 (3–12)). Of the total 133 randomised trials, 36 (27%) had OS and 72 (54%) had PFS as a primary endpoint, whereas, of the 61 non-randomised studies, 58 (97%) listed response rate as the primary endpoint. The randomised cohort consisted mostly of phase III studies with a higher accrual rate (phase III: 120 (89%); accrual rate, (IQR): 24 (17–38)). While Roche sponsored 18 of 133 (8%) studies in the randomised cohort, Merck had the highest accrual rate (accrual rate (IQR): 35 (18–47)). Randomised studies were more likely to have a higher number of investigational sites (135 sites (95–189)) versus non-randomised (47 sites (30–67)).

Poisson regression analysis results

Table 3 reports the results from the regression analyses per randomised and non-randomised analysis cohorts. In the randomised adjusted model, the accrual rate was 2.13 (95% CI 1.48 to 2.99) times higher in phase III trials compared with early phase trials, adjusting for other covariates. The accrual rate was 1.55 (95% CI 1.18 to 2.09) times higher in trials investigating first and second line drugs compared with trials testing agents in the third line and beyond. A study sponsored by Merck was associated with 1.47 (95% CI 1.18 to 2.37) times higher accrual rate compared with all 'other' manufacturers in the cohort. In contrast, primary endpoints, crossover, response rate, the number of investigational sites, disease burden and the randomisation ratio used were not associated with the rate of accrual. In the non-randomised adjusted model, only the type of manufacturer was associated with accrual rate. The accrual rate was 2.03 (95% CI 1.10 to 3.92) times higher for clinical trials sponsored by Merck, compared with all 'other' manufacturers. Trials sponsored by Pfizer were associated with 0.17 (95% CI 0.05 to 0.75) times lower accrual rate, compared with all other manufacturers. Primary endpoint, crossover, trial phase, response rate, the number of investigational sites, disease burden and line of therapy were not associated with the rate of accrual.

Secondary analysis

Our secondary analysis included a convenience sample of 146 randomised clinical trials from a distinct dataset. Summary statistics are available in online supplemental table S1. The median accrual rate was 23 persons per month (IQR: 14–36) and sample size was 510 participants (IQR: 307–719). Of the 146 trials, 129 were phase III trials (89%) and 123 were investigating medicines in the first or second lines of treatment (n=123 (84%)). Merck sponsored 16 (11%) of the 146 trials and had a higher accrual rate (rate (IQR): 41 (32–49)) compared with Pfizer, Novartis, Roche and 'other' manufacturers. In the adjusted regression analysis, the accrual rate was 3.14 (95% CI 2.06 to 4.73) times higher for phase III trials compared with early phase trials. A trial sponsored by Merck was associated with an accrual rate 1.49 (95% CI 1.02 to 2.22) times higher compared with 'other' manufacturers, and the number of sites was associated with an accrual rate 1.01 (95% CI 0.99 to 1.01) times higher. Trials investigating therapies in first or second-line settings were associated with an accrual rate 1.43 (95% CI 104 to 2.02) times higher compared with third line or beyond.

Table 1 Descriptive characteristics and accrual rate among clinical trials supporting oncology US Food and Drug Administration approvals (n=194)

	All studies		
Trial characteristics	**N (%)**	**Accrual rate (IQR)***	**P value†**
Total studies	194 (100)	17 (7–32)	<0.001
Sample size			
Median (IQR)	371 (209–574)		NA
Duration of enrolment (months)			
Median (IQR)	22 (16–31)		NA
RCT			
Yes	133 (68)	22 (16–31)	<0.001
No	61 (32)	5 (3–12)	
Blinding			
Less than double blind	148 (76)	14 (5–23)	<0.001
Double blind and over	46 (24)	32 (18–41)	
Primary endpoint			
OS	37 (19)	22 (18–35)	<0.001
PFS	74 (38)	21 (13–36)	
Response rate	83 (43)	7 (4–17)	
Phase			
I/II	69 (36)	6 (3–12)	<0.001
III	125 (64)	23 (17–37)	
Line of therapy			
First or second line	162 (84)	18 (7–34)	0.002
Third line or beyond	32 (16)	13 (5–19)	
Manufacturer			
Pfizer	14 (7)	16 (7–30)	
Roche	21 (11)	19 (15–36)	
Novartis	12 (7)	14 (8–32)	<0.001
Merck	20 (10)	21 (13–37)	
All else	127 (65)	17 (6–28)	
Randomisation ratio			
Equal	95 (49)	23 (15–36)	
Skewed	38 (20)	21 (15–35)	<0.001
NA‡	61 (31)	5 (3–12)	
Crossover specified			
Yes	56 (29)	26 (17–41)	<0.001
No	138 (71)	14 (5–23)	
Single agent response rate			
Median (IQR)	44% (23–64)		NA
Sites, number			
Median (IQR)	109 (55–165)		NA
Disease burden‡			
Median (IQR)	23 660 (13 780–43 600)		NA

*Accrual rate: reported as median accrual rate; persons per month accrued.
†P value from Wilcoxon signed-rank test and χ^2 test for categorical variables.
‡Disease burden: number of deaths in 1 year per tumour type using data from Surveillance, Epidemiology and End Results.[16]
NA, not applicable; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial.

Table 2 Descriptive characteristics and accrual rate among randomised and non-randomised clinical trials supporting oncology US Food and Drug Administration approvals

	Randomised			Non-randomised		
Trial characteristics	**N (%)**	**Accrual rate (IQR)***	**P value†**	**N (%)**	**Accrual rate (IQR)***	**P value†**
Total number	133 (100)		NA	61 (100)		NA
Sample size			NA			NA
Median (IQR)	466 (319–669)			105 (74–206)		
Duration of enrolment (months)			NA			NA
Median (IQR)	22 (16–27)			22 (14–34)		
Accrual rate			NA			NA
Median (IQR)	22 (15–36)			5 (3–12)		
Blinding						
Less than double blind	87 (65)	20 (13–32)	0.008	61 (100)	5 (3–12)	NA
Double blind and over	46 (35)	32 (18–41)		0 (0)	0 (0)	
Primary endpoint						
OS	36 (27)	22 (18–36)		1 (0)	16 (16–16)	
PFS	72 (54)	21 (14–36)	0.007	2 (3)	8 (6–10)	<0.001
Response rate	25 (19)	23 (13–35)		58 (97)	5 (3–11)	
Phase						
1/2	13 (11)	10 (6–15)	0.005	56 (92)	5 (3–12)	<0.001
3	120 (89)	24 (17–38)		5 (8)	6 (4–7)	
Line of therapy						
First or second line	115 (86)	24 (17–39)		47 (77)	5 (3–8)	
Third line or beyond	18 (14)	16 (13–20)	0.002	14 (23)	5 (2–13)	0.118
Manufacturer						
Pfizer	12 (9)	19 (12–33)		2 (3)	2 (2–3)	
Roche	18 (14)	21 (17–38)		3 (5)	5 (4–14)	<0.001
Novartis	7 (5)	24 (16–34)	<0.001	5 (8)	4 (2–9)	
Merck	11 (8)	35 (18–47)		9 (15)	13 (6–19)	
All else	85 (64)	21 (15–34)		42 (69)	4 (3–8)	
Randomisation ratio						
Equal	95 (71)	23 (15–36)		0 (0)	0 (0)	
Skewed	38 (29)	21 (15–35)	0.03	0 (0)	0 (0)	NA
NA‡	0 (0)	0 (0)		61 (100)	5	
Crossover specified						
Yes	55 (41)	28 (19–41)	0.03	1 (1)	14 (14–14)	0.006
No	78 (59)	20 (14–32)		60 (99)	5 (3–11)	
Single agent response rate						
Median (IQR)	44% (22–65)		NA	44% (31–62)		NA
Sites, number						
Median (IQR)	135 (95–189)		NA	47 (30–67)		NA
Disease burden§						
Median (IQR)	23 660 (13 780–43 600)		NA	20 720 (13 780–34 130)		NA

*Accrual rate: reported as median accrual rate; persons per month accrued.
†P value from Wilcoxen Signed Rank test and x^2 test for categorical variables
‡Non-randomised studies do not have a randomisation ratio.
§Disease burden: number of deaths in 1 year per tumour type using data from Surveillance, Epidemiology and End Results.[16]
NA, not applicable; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial.

Table 3 Factors associated with clinical trial accrual in randomised and non-randomised studies supporting oncology US Food and Drug Administration approvals, Poisson regression results

	Study cohorts					
	Randomised			Non-randomised*		
Variable	Rate ratio	95% CI	P value	Rate ratio	95% CI	P value
Blinding						
Less than double blind	Reference	Reference	Reference	Not included		
Double blind	1.21	0.97 to 1.50	0.07			
Endpoint						
Response rate	Reference	Reference	Reference	Reference	Reference	Reference
PFS	0.82	0.62 to 1.08	0.15	1.97	0.57 to 9.03	0.32
OS	0.94	0.68 to 1.29	0.68	2.51	0.71 to 19.14	0.25
Crossover						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.18	0.96 to 1.45	0.1	1.69	0.35 to 14.67	0.55
Phase						
Phase 1/2	Reference	Reference	Reference	Reference	Reference	Reference
Phase 3	2.13	1.48 to 2.99	<0.01	0.94	0.43 to 2.32	0.89
Line						
Third line or beyond	Reference	Reference	Reference	Reference	Reference	Reference
First and second line	1.55	1.15 to 2.04	0.01	1.09	0.62 to 1.84	0.75
Single agent response rate	1.09	0.74 to 1.64	0.64	0.7	0.25 to 1.98	0.54
Sites	1	0.99 to 1.00	0.52	1	0.99 to 1.01	0.11
Manufacturer						
Other	Reference	Reference	Reference	Reference	Reference	Reference
Pfizer	0.76	0.53 to 1.07	0.12	0.18	0.05 to 0.75	0.01
Roche	1.02	0.76 to 1.37	0.91	1.13	0.45 to 3.49	0.8
Novartis	0.9	0.59 to 1.43	0.63	1.22	0.57 to 2.90	0.61
Merck	1.47	1.18 to 2.37	0.03	2.03	1.10 to 3.92	0.03
Disease burden†	0.99	0.99 to 1.00	0.13	1	0.99 to 1.00	0.12
Randomisation ratio						
Equal	Reference	Reference	Reference	Not included		
Skewed	0.87	0.69 to 1.09	0.21			

*Certain variables were excluded in the regression model of non-randomised studies if they were deemed collinear.
†Disease burden: number of deaths in 1 year per tumour type using data from Surveillance, Epidemiology and End Results.[16]
OS, overall survival; PFS, progression-free survival.

Covariates such as blinding, primary endpoint, crossover, response rate, disease burden and randomisation ratio were not associated with accrual rate. The results of the adjusted secondary analysis are reported in online supplemental table S2.

DISCUSSION

We sought to examine factors associated with accrual rate using a cohort of recent clinical trials leading to US FDA cancer drug approvals from 2015 to 2020. We considered randomised and non-randomised studies separately given certain variables that were not pertinent to both cohorts (ie, randomisation ratio and blinding). We then confirmed our results in a secondary dataset of clinical trials published in the top six journals from 2018 to 2020. We found that earlier lines of therapy (first and second), phase of study (phase III), and specific manufacturers (Merck, Pfizer (non-randomised)) were the only factors associated with accrual rate. This effect was consistent across randomised and non-randomised studies, and again in our confirmatory analysis.

At the same time, many proffered enticement factors for trial accrual failed to demonstrate association in multivariable analysis. The ratio of randomisation (1:1

vs 1:2 or 3:2), presence of crossover, promise of a drug (reflected by single agent response rate), number of investigational sites and population disease burden (market share) were not associated with the rate of accrual. These important negative findings are similar to other studies. For example, Bennette *et al* also found no association between study blinding and annual incidence of disease with participant accrual.[11] Paul *et al* examined factors associated with adequate accrual in published trials for solid malignancies between 2000 and 2006 and found age, randomisation, blinding and specialty were not associated with sufficient accrual.[18] Finally, Chen and Prasad also found no association between trial accrual rate and studies with crossover designs despite an indication that patients prefer open-label and crossover designs, which ought to encourage enrolment.[8 14] This is an important finding with strong implications.

The most parsimonious explanation for our study results is that companies construct or contract with large research enterprises to run pivotal trials. Each company builds a network of hospitals, locations and physicians with whom they work. Trials might accrue at a higher rate (more participants enrolled per month) in a treatment naïve (first line) or early treatment (second line) setting than with later lines. Some companies might be more efficient in their accrual based on increased networks (ie, Merck). At the same time, the research enterprise is largely insensitive to commonly touted metrics of enticement. Offering crossover to the investigational drug does not speed accrual. A favourable randomisation ratio (ie, 2:1 or 3:2) does not speed accrual. Even the initial promise of the drug (single agent response rate); the primary endpoint of the study, and so on. This suggests that these enticements are not the constraint of the current trials system.

We found the rate of accrual was approximately 1.5 times higher in studies investigating first and second line medicines compared with studies for third line therapeutics or beyond in randomised studies. First and second line drugs comprise of the largest proportion of the pharmaceutical market share.[19] There is a larger proportion of eligible patients who meet the criteria to enter first and second line studies which may also contribute to accrual. As one advances in lines of therapy, the pool of eligible patients becomes smaller, as many, unfortunately, may die.

The accrual rate was two to three times higher for phase III studies compared with early phase studies in the randomised and secondary analyses. However, this effect was not significant in the non-randomised cohort. This finding is likely related to the distribution of our sample of industry-sponsored, successfully accrued studies. As an investigational drug moves through the development stages (ie, preclinical to phase III), it is more likely to be successful in prior studies. Therefore, our sample might be biased towards the top performing agents that are more likely to generate returns for sponsors.

We found a trial sponsored by Merck had nearly 1.5 times higher accrual rate compared with 'other' manufacturers. It is not immediately clear why Merck enjoys this advantage. According to annual filings with the US Securities and Exchange Commission, Merck is the fourth largest manufacturer of cancer medicines.[15] However, the company is unique as it experienced substantial growth in recent years compared with other pharmaceutical manufacturers. From 2016 to 2019, their drug Pembrolizumab generated 12% of their total oncology revenue (3% of total revenue) and is poised to be one of the top 15 best-selling cancer drugs in 2022.[20] Within our study period, pembrolizumab received widespread approval across multiple indications which included numerous clinical trials which might account for the significant association.[21] Nevertheless, the academic community would benefit from further investigation into the mechanisms for which Merck and other industry sponsors accrue study participants.

Strengths and limitations

Our cross-sectional study has strengths and limitations. It is unique as it is the first evaluation of factors associated with accrual rate in industry sponsored clinical trials supporting FDA cancer drug approvals. This is a special set of studies that warrant attention because they lead to the marketing authorisation of new products. Yet, we encountered limitations. First, our sample reflects a selective cohort of industry-sponsored clinical trials that have successfully accrued patients and reached positive results. We did not examine factors associated with trials with failed accrual. Future research might focus on a comparison of successful (completed) versus unsuccessful (delayed or stopped) trials. Second, we extracted explanatory variables from publications associated with the FDA approval. If studies were not listed on ClinicalTrials.Gov or included in the approval notice, it might not be included. Further, we did not include updated studies published afterward. However, because we were interested in trial-level features of these studies, updated results (ie, survival gain, or cost-effectiveness analyses) would not alter our results. Further, our findings were similar across three analyses with two distinct datasets, increasing the confidence in our findings. To ensure accuracy of our data extraction, we searched all supplemental information, appendices and trial protocols. While we included factors associated with accrual in our model based on current literature, it could also occur that not all relevant explanatory variables were incorporated in our analyses. Finally, the purpose of this research was to understand factors associated with accrual rate. Future research might understand the effect and interaction of these variables.

CONCLUSIONS

Low participation rates and subsequent closure of clinical trials have received widespread attention, including in popular media where the landscape of oncology studies

were deemed to be in an 'a state of crisis'.[22] Despite numerous studies examining association, barriers, and predictors of accrual, participation in oncology trials remains low. In this cross-sectional study, we found important factors previously believed to entice patients to enrol in clinical trials such as disease burden, primary endpoint, crossover, randomisation ratio, blinding, single-agent response rate, were not associated with accrual rate. The factors associated with accrual rate in oncology clinical trials are insensitive to important patient-centred characteristics, and likely represent the ability of sponsors to build and nurture a global clinical trial apparatus.

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Contributors KJ lead the analysis, drafting and disseminationnd takes responsibility for the analysis. KJ and AH had access to the data and analysis. AH, MM, VP and TO were involved in the initial drafting and editing of the manuscript. VP was responsible for supervision and conceptualisation.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data requests can be made to KJ, kjenei@mail.ubc.ca.

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