Patient enrollment per month (accrual) in clinical trials leading to the FDA approval of new cancer drugs

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Supplementary Online Material

This supplementary material has been provided by the authors to give readers additional information about their work.

		(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)
(1)	**Accrual rate**	1.00																	
(2)	**Trial design**	-0.43	1.00																
(3)	**Sponsor**	-0.12	-0.01	1.00															
(4)	**#Sites**	0.59	-0.45	-0.04	1.00														
(5)	**#Countries**	0.55	-0.53	-0.31	0.60	1.00													
(6)	**Innovativeness**	-0.26	0.23	0.03	-0.19	-0.23	1.00												
(7)	**MoA**	0.03	0.08	-0.06	-0.03	0.06	0.02	1.00											
(8)	**Biomarker**	0.02	0.05	0.06	0.10	0.13	-0.07	-0.13	1.00										
(9)	**Line**	-0.23	0.35	-0.10	-0.16	-0.19	0.14	0.03	-0.13	1.00									
(10)	**Treatment**	-0.29	0.39	-0.09	-0.23	-0.23	0.18	-0.06	0.03	0.25	1.00								
(11)	**Disease**	0.28	-0.30	-0.04	0.27	0.28	-0.03	-0.03	0.22	-0.22	-0.09	1.00							
(12)	**DALY**	0.21	-0.21	-0.06	0.18	0.24	-0.12	-0.06	0.32	-0.16	-0.07	0.46	1.00						
(13)	**Orphan**	-0.36	0.23	0.07	-0.35	-0.26	0.16	-0.05	-0.07	0.07	0.17	-0.53	-0.37	1.00					
(14)	**Phase**	0.48	-0.81	-0.01	0.49	0.58	-0.27	-0.08	-0.10	-0.28	-0.30	0.22	0.14	-0.21	1.00				
(15)	**Blinding**	0.26	-0.44	-0.04	0.32	0.33	-0.09	-0.10	-0.06	-0.16	-0.11	0.29	0.04	-0.12	0.43	1.00			
(16)	**Comparator**	-0.19	0.41	0.07	-0.18	-0.27	0.12	-0.01	-0.03	0.20	-0.01	-0.11	-0.13	0.16	-0.42	0.28	1.00		
(17)	**Randomization**	-0.08	-0.06	-0.09	0.00	-0.08	0.07	-0.18	0.05	0.14	0.24	0.20	-0.01	-0.03	0.07	0.35	0.14	1.00	
(18)	**Crossover**	0.28	-0.42	-0.04	0.31	0.31	-0.07	-0.04	0.04	-0.17	-0.17	0.19	0.15	-0.15	0.39	0.29	-0.20	0.11	1.00

Table e1. Pairwise Pearson correlation coefficients

Abbreviations: DALYs, disability-adjusted life years; FDA, US Food and Drug Administration; MoA, mechanism of action.

	Industry -Sponsored	Government -Sponsored	*P value*
Background factors			
No. of trial sites	97 (39-151)	43 (13-163)	*0.034*
No. of trial countries	16 (9-22)	2 (1-3)	*<.001*
Treatment-related factors			
Indication innovativeness [a]			*0.800*
Addition-in-Indication	65 (15)	3 (11)	
Advance-in-Indication	199 (46)	12 (44)	
First-in-Indication	164 (38)	12 (44)	
Mechanism of action			*0.347*
Cytotoxic chemotherapy	29 (7)	3 (11)	
Targeted therapies	255 (60)	18 (67)	
Immune regulators	144 (34)	6 (22)	
Biomarker			*0.221*
No	274 (64)	14 (52)	
Yes	154 (36)	13 (48)	
Line of therapy			*0.048*
First-line	199 (46)	18 (67)	
Advanced-line	229 (54)	9 (33)	
Treatment type			*0.061*
Combination therapy	143 (33)	14 (52)	
Monotherapy	285 (67)	13 (48)	
Disease-related factors			
Cancer disease			*0.530*
Hematologic	143 (33)	11 (41)	
Solid	285 (67)	16 (59)	
DALYs	117 (24-428)	107 (69-130)	*0.456*
FDA Orphan Designation			*0.153*
Non-orphan	155 (36)	6 (22)	
Orphan	273 (64)	21 (78)	
Reformed Orphan Designation [b]			*0.069*
Non-orphan	155 (36)	6 (22)	
Common orphan	63 (15)	1 (4)	
Rare orphan	187 (44)	18 (67)	
Ultra-rare orphan	23 (5)	2 (7)	
Trial design			
Phase			*0.841*
Phase 1/2	177 (41)	12 (44)	
Phase 3	251 (59)	15 (56)	
Allocation			*0.839*
Randomized	274 (64)	18 (67)	
Single-arm	154 (36)	9 (33)	
Masking			*0.498*
Open-label	317 (116)	22 (122)	
Double blind	111 (41)	5 (28)	
Comparator			*0.160*
Active	104 (38)	3 (17)	
Placebo / no treatment	324 (118)	24 (133)	
Randomization			*0.169*
Equal	189 (69)	16 (89)	
Skewed	73 (27)	2 (11)	
Crossover [c]			*0.321*
Not specified	143 (52)	10 (56)	
Allowed	62 (23)	6 (33)	
Not allowed	69 (25)	2 (11)	
Total	**428 (100)**	**27 (100)**	

Table e2. Comparison of industry-and government-sponsored trials

[a] 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".

[b] Orphan indications were further stratified according to the number of affected US inhabitants into common (>200,000), rare (200,000-6,600), and ultra-rare (<6,600).

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

Abbreviations: DALY, disability-adjusted life year; FDA, US Food and Drug Administration.

	Adjusted Rate Ratio	(95% CI)	*P value*
Background factors			
Trial sponsor			
Industry	1	Reference	
Government	0.80	(0.57-1.13)	*0.207*
No. of trial sites [a]	1.001	(1.001-1.002)	*0.000*
No. of trial countries [a]	1.02	(1.01-1.03)	*0.000*
Treatment-related factors			
Indication innovativeness [b]			
Addition-to-Indication	1	Reference	
Advance-in-Indication	0.84	(0.7-1.02)	*0.082*
First-in-Indication	0.78	(0.63-0.98)	*0.034*
Mechanism of action			
Cytotoxic chemotherapy	1	Reference	
Targeted therapies	1.00	(0.75-1.33)	*0.986*
Immune regulators	1.08	(0.8-1.46)	*0.610*
Biomarker			
No	1	Reference	
Yes	0.88	(0.75-1.03)	*0.102*
Line of therapy			
First-line	1	Reference	
Advanced-line	0.81	(0.69-0.95)	*0.010*
Treatment type			
Combination therapy	1	Reference	
Monotherapy	0.81	(0.69-0.95)	*0.010*
Disease-related factors			
FDA Orphan Designation [c]			
Non-orphan	1	Reference	
Common orphan	0.89	(0.69-1.15)	*0.356*
Rare orphan	0.72	(0.61-0.86)	*0.000*
Ultra-rare orphan	0.30	(0.24-0.37)	*0.000*
FDA approval			
FDA approval type			
Standard approval	1	Reference	
Accelerated approval	1.12	(0.82-1.54)	*0.465*
Trial design			
Phase			
Phase ½	1	Reference	
Phase 3	1.73	(1.05-2.85)	*0.030*
Masking			
Open-label	1	Reference	
Double blind	1.04	(0.81-1.34)	*0.745*
Comparator			
Active	1	Reference	
Placebo / no treatment	0.99	(0.76-1.29)	*0.933*
Randomization [d]			
Equal	1	Reference	
Skewed	0.96	(0.81-1.15)	*0.659*
Crossover			
Not specified	1	Reference	
Allowed	1.14	(0.97-1.35)	*0.116*
Not allowed	1.13	(0.97-1.32)	*0.116*

Table e3. Multivariable Poisson regression including accelerated approval in randomized trials

[a] For interval-scaled variables, Poisson correlation coefficients are presented in the univariate 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] Orphan indications were further stratified according to the number of affected US inhabitants into common (>200,000), rare (200,000-6,600), and ultra-rare (<6,600).

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

Abbreviations: FDA, US Food and Drug Administration.

	Adjusted Rate Ratio	(95% CI)	*P value*
Background factors			
Trial sponsor			
Industry	1	Reference	
Government	0.63	(0.23-1.77)	*0.384*
No. of trial sites [a]	1.007	(1.002-1.012)	*0.007*
No. of trial countries [a]	0.998	(0.966-1.03)	*0.888*
Treatment-related factors			
Indication innovativeness [b]			
Addition-to-Indication	1	Reference	
Advance-in-Indication	1.33	(0.9-1.95)	*0.150*
First-in-Indication	1.01	(0.65-1.57)	*0.957*
Mechanism of action			
Cytotoxic chemotherapy	1	Reference	
Targeted therapies	1.68	(0.83-3.37)	*0.147*
Immune regulators	2.40	(1.21-4.73)	*0.012*
Biomarker			
No	1	Reference	
Yes	0.80	(0.48-1.34)	*0.391*
Line of therapy			
First-line	1	Reference	
Advanced-line	1.31	(0.92-1.87)	*0.133*
Treatment type			
Combination therapy	1	Reference	
Monotherapy	1.39	(0.86-2.26)	*0.180*
Disease-related factors			
FDA Orphan Designation [c]			
Non-orphan	1	Reference	
Common orphan	0.76	(0.44-1.31)	*0.321*
Rare orphan	0.77	(0.55-1.09)	*0.145*
Ultra-rare orphan	0.62	(0.4-0.95)	*0.028*
FDA approval			
FDA approval type			
Standard approval	1	Reference	
Accelerated approval	1.31	(0.97-1.77)	*0.079*
Trial design			
Phase			
Phase 1/2	1	Reference	
Phase 3	1.29	(0.78-2.14)	*0.328*

Table e4. Multivariable Poisson regression including accelerated approval in single-arm trials

[a] For interval-scaled variables, Poisson correlation coefficients are presented in the univariate 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] Orphan indications were further stratified according to the number of affected US inhabitants into common (>200,000), rare (200,000-6,600), and ultra-rare (<6,600).

Abbreviations: FDA, US Food and Drug Administration.