Updated Analysis of Pediatric Clinical Trials Registered in ClinicalTrials.gov, 2008-2019

Yang Zhong
Department of Epidemiology and Health Statistics, West China School of Public Health and West China fourth Hospital, Sichuan University, Sichuan

Li-jun Zhou
Sichuan Center for Disease Control and Prevention, Chengdu, Sichuan

Lei Li
Department of Anesthesiology, Chengdu Women's and Children's Central Hospital, Chengdu, Sichuan

Tao Zhang (statzhangtao@scu.edu.cn)
Department of Epidemiology and Health Statistics, West China School of Public Health and West China fourth Hospital, Sichuan University, Sichuan

Xingyu Zhang
Department of Systems, Populations and Leadership University of Michigan School of Nursing 400 North Ingalls Building, Ann Arbor, MI

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Abstract

Background Since the national clinical trials registry (ClinicalTrials.gov) launched in February 2000, more than 300,000 trials have been registered. However, little is known about the registered pediatric clinical trials with regarding to characteristics, trends and quality over time.

Methods To describe patterns of the registered pediatric clinical trials, a dataset of trials involving children was downloaded from ClinicalTrials.gov on August 1st, 2020. To further trace the registration of pediatric disease types, we selected the top four infectious diseases to describe their trends over time. To examine reporting completion rate of clinical trial results, we identified completed studies and then observed the proportion of trials subject to reporting.

Results Between 2000 and 2019, a total of 53,060 pediatric trials were registered at ClinicalTrials.gov, including 36,136 (68.1%) interventional trials and 6,692(31.5%) observational trials. The number of them increased significantly over time. Meanwhile, the number of missing data elements has generally declined.Most interventional pediatric trials were single center (61.4%), small-scale(58.9%), randomized (66.0%), and none masking(56.9%), with fewer drug trials being conducted over time.Many pediatric clinical trials were funded by other organizations.The proportion of trials complianced with reporting results varied by study type, trial phase and lead sponsor.

Conclusion The pediatric clinical trial registration are on the rise, with significant changes in registration information such as trial type, main purpose, and intervention characteristics, which can help stakeholders inform the decision to conduct trials in children. Although the proportion of missing data was decreasing, the proportion of reporting results remained to be improved.

Introduction

Clinical trials are considered the gold standard for assessing the safety and effectiveness of new therapies and for generating evidence-based knowledge in medicine [1]. However, because of the unique nature of the pediatric population, safety concerns, stringent ethical requirements, and lack of commercial interest, research with adults cannot just be generalized or extrapolated to pediatric populations in most cases [2] [3] [4] [5]. To make evidence-based treatment decisions, focusing on pediatric clinical trials that adapt well to the patient population as well as pediatric diseases and therapeutic areas is important.

The creation of ClinicalTrials.gov in 2000 provides significant insights into the state of pediatric clinical trials. The policy obliges sponsors or trial designers to register trials and record key data elements (effective September 27, 2007), report basic results (September 27, 2008), and report adverse events (September 27, 2009) [6] [7] [8].

Most previous studies have examined fundamental characteristics of interventional clinical trials registered in the ClinicalTrials.gov database or profiled registered clinical trials for specific diseases [9] [10] [11]. From January 2008 to December 2019, 53,060 clinical trials involving children have been registered in

the ClinicalTrials.gov database, but a comprehensive description of the character and quality of the information provided in this process is rare.

In this article, we sought to complete an updated analysis of pediatric clinical trials, describing their fundamental characteristics and the state of results reporting at ClinicalTrials.gov.

Data Source

A data set of 53,060 pediatric clinical trials registered at ClinicalTrials.gov was downloaded on August 1st, 2020. The data set was locked, and a relational database was subsequently designed to facilitate analysis.

Data Collection

Our analysis was focused on pediatric clinical trials registered with ClinicalTrials.gov between January 2008 and December 2019. We used the “study type” field from the ClinicalTrials.gov registry, which included the following choices: interventional, observational, expanded access, and not available (NA). We focused in particular on interventional and observational trials. Interventional studies were regrouped according to the 4 clinical specialties: infectious disease, cancer, immune disease, and respiratory disease. Within these specialty data sets, a few data elements are missing because of limitations in the data set or logistical problems in obtaining analyzable information.

Analysis

We report primarily descriptive statistics. No formal statistical comparison was made due to the descriptive nature of the study.

Results

Characteristics for All Studies

From January 2008 to December 2019, a total of 53,060 pediatric trials were registered at ClinicalTrials.gov, including 36,136 interventional trials (68.1%), 16,692 observational trials (31.5%) and 232 expansibility trials (0.4%). These trials provide a 12-year period for studying trends in registered trials. We examined trends by primary purpose, intervention type, enrollment, masking, allocation status, Lead sponsor as well as by stratifying the trials into four time periods ([2008–2010], [2011–2013], [2014–2016], [2017–2019]). A summary of interventional and obsevational trials, and selected subcategories is presented in Table 1–2.

Table 1
Characteristics for Interventional Trials Registered in ClinicalTrials.gov, 2008–2019

	Trials, No. (%)				
	All, 2008–2019 (n = 36 136)	2008–2010 (n = 7 029)	2011–2013 (n = 7 486)	2014–2016 (n = 9 883)	2017–2019 (n = 11 738)
Primary purpose					
Treatment	21 126(60.0)	4608(68.1)	4476(62.7)	5614(58.7)	6428(54.8)
Prevention	6 110(17.4)	1227(18.1)	1376(19.3)	1514(16.2)	1962(16.7)
Supportive Care	1 938(5.5)	264(3.9)	360(5.0)	583(6.1)	731(6.2)
Other	6 026(17.1)	669(3.3)	922(12.9)	1823(19.1)	2612(22.3)
Missing	936(2.6)	261(3.7)	352(4.7)	318(3.2)	5(0.0)
Intervention type					
Drug	13348(36.9)	3427(48.8)	3066(41.0)	3457(35.0)	3398(28.9)
Behavioral	6194(17.1)	889(12.6)	1171(15.6)	1739(17.6)	2395(20.4)
Device	4325(12.0)	570(8.1)	709(9.5)	1457(14.7)	1589(13.5)
Procedure	3366(9.3)	658(9.4)	709(9.5)	952(9.6)	1047(8.9)
Biological	3011(8.3)	759(10.8)	673(9.0)	756(7.6)	823(7.0)
Dietary supplement	1623(4.5)	353(5.0)	381(5.1)	446(4.5)	443(3.8)
Genetic	191(0.5)	33(0.5)	37(0.5)	48(0.5)	73(0.6)
Radiation	383(1.1)	91(1.3)	77(1.0)	109(1.1)	106(0.9)
Other	7409(20.5)	1015(14.4)	1412(18.9)	1 015(14.4)	2757(23.5)
Enrollment					
1-100	20 614(58.9)	3820(56.8)	4158(58.1)	5758(59.5)	6940(60.0)
101–1000	11 995(34.2)	2461(36.6)	2490(34.8)	3251(33.6)	3828(33.1)
>1000	2 417(6.9)	4438(6.6)	515(7.2)	668(6.9)	798(6.9)
Masking					
None	20 426(56.9)	3923(56.6)	4 116(55.4)	5 765(58.6)	6 622(56.5)
Single	5 757(16.0)	922(13.3)	1 192(16.0)	1 600(16.3)	2 043(17.4)
Double	3 523(9.8)	681(9.8)	655(8.8)	881(9.0)	1 306(11.1)

Abbreviations: NIH, National Institutes of Health.

	Trials, No. (%)				
Triple	2 427(6.8)	486(7.0)	567(7.6)	599(6.1)	775(6.6)
Quadruple	3 783(10.5)	914(13.2)	904(12.2)	991(10.1)	974(8.3)
Missing	220(0.6)	103(1.5)	52(0.7)	47(0.5)	18(0.2)
Allocation status					
Randomized	23 643(66.0)	4 618(66.8)	4 976(66.9)	6 387(64.9)	7 662(65.7)
Nonrandomized	3 869(10.8)	936(13.5)	740(10.0)	1 029(10.5)	1 164(10.0)
N/A	8 327(23.2)	1 356(19.6)	1 718(23.1)	2 418(24.6)	2 835(24.3)
Missing	297(0.8)	119(1.7)	52(0.7)	49(0.5)	77(0.7)
Lead sponsor					
Industry	7101(19.7)	1909(27.2)	1589(21.2)	1779(18.0)	1824(15.5)
NIH	469(1.3)	166(2.4)	102(1.4)	95(1.0)	106(0.9)
US federal	220(0.6)	66(0.9)	41(0.5)	74(0.5)	66(0.6)
Other	28346(78.4)	4888(69.5)	5754(76.9)	7962(80.6)	9742(83.0)

Abbreviations: NIH, National Institutes of Health.

Table 2
Characteristics for Observational Trials Registered in ClinicalTrials.gov, 2008–2019

	Trials, No. (%)				
	All, 2008–2019 (n = 16 692)	2008–2010 (n = 3116)	2011–2013 (n = 3295)	2014–2016 (n = 4125)	2017–2019 (n = 6156)
Intervention type					
Drug	1524(18.2)	346(24.9)	392(29.0)	377(16.8)	409(12.0)
Behavioral	377(4.5)	60(4.3)	55(4.1)	81(3.6)	181(5.3)
Device	1121(13.4)	136(9.8)	171(12.7)	305(13.6)	509(15.0)
Procedure	1128(13.4)	196(14.1)	160(11.8)	302(13.4)	470(13.8)
Biological	291(3.5)	74(5.3)	55(4.1)	80(3.6)	82(2.4)
Dietary supplement	61(0.7)	5(0.4)	10(0.7)	21(0.9)	25(0.7)
Genetic	312(3.7)	121(8.7)	71(5.3)	50(2.2)	70(2.1)
Radiation	97(1.2)	12(0.9)	6(0.4)	26(1.2)	53(1.6)
Other	3476(41.4)	440(31.7)	431(31.9)	1007(44.8)	1598(47.0)
Enrollment					
1-100	6618(40.7)	1185(40.5)	1339(41.9)	1487(36.8)	2607(42.7)
101–1000	6512(40.0)	1175(40.1)	1252(39.1)	1712(42.4)	2373(38.9)
>1000	3136(19.3)	569(19.4)	608(19.0)	840(20.8)	1119(18.3)
Time Perspective					
Prospective	10951(67.2)	2055(70.2)	2230(69.9)	2824(69.9)	3842(62.5)
Retrospective	2768(17.0)	453(15.5)	554(17.4)	639(15.8)	1122(18.2)
Cross-Sectional	1985(12.2)	349(11.9)	327(10.3)	461(11.4)	848(13.8)
Other	602(3.7)	69(2.4)	78(2.4)	117(2.9)	338(5.5)
Missing	386(2.3)	190(6.1)	106(3.2)	84(2.0)	6(0.1)
Observational Model					
Case-Control	2204(14.0)	429(15.8)	482(16.2)	559(14.4)	734(11.9)
Case-Crossover	156(1.0)	32(1.2)	30(1.0)	33(0.8)	61(1.0)
Case-Only	2612(16.6)	604(22.2)	563(19.0)	547(14.1)	898(14.6)

Abbreviations: NIH, National Institutes of Health.

	Trials, No. (%)				
Cohort	9064(57.6)	1438(52.9)	1687(56.9)	2391(61.4)	3548(57.7)
Ecologic or Community	300(1.9)	58(2.1)	52(1.8)	67(1.7)	123(2.0)
Family-Based	187(1.2)	59(2.2)	26(0.9)	46(1.2)	56(0.9)
Other	1202(7.6)	98(3.6)	127(4.3)	248(6.4)	729(11.9)
Missing	967(5.8)	398(12.8)	328(10.0)	234(5.7)	7(0.1)
Lead sponsor					
Industry	2899(17.4)	728(23.4)	785(23.8)	713(17.3)	673(10.9)
NIH	368(2.2)	124(4.0)	97(2.9)	88(2.1)	59(1.0)
US federal	38(0.2)	13(0.4)	9(0.3)	7(0.2)	9(0.1)
Other	13387(80.2)	2251(72.2)	2404(73.0)	3317(80.4)	5415(88.0)
Abbreviations: NIH, National Institutes of Health.					

Among the changes in the number of subgroups over time, we can see that registered clinical trials, especially interventional trials, showed a significant increase in number over the four time periods. The number of missing data elements declined across some characteristics. The rate of registered interventional trials that do not report a primary purpose decreased from 3.7–0.0%; those that do not report enrollment decreased from 4.3–1.5%; those that do not report masking decreased from 1.5–0.2%; and those that do not report allocation status decreased from 1.7–0.7%. The same downward trends of missing data were observed in the observational trials with regard to enrollment (which declined from 6.0–0.9%), time perspective (which declined from 6.1–0.1%) and obsevational model (which declined from 12.8–0.1%).

The primary purpose was “treatment” in the majority of interventional trials (60.0%). In terms of intervention types, drug intervention was the main type (36.9%), and the drug intervential type trials showed a decreasing trend (from 48.8–28.9%). Meanwhile, the proportion of behavioral intervention trials increased from 12.6–20.4%. In contrast, in observational trials, we observed an increase in the number of registrations of device intervention types. The majority of interventional trials were small in terms of number of participants. As is presented, 93.1% of interventional trials had an anticipated enrollment of 1000 or fewer participants, and 58.9% had 100 or fewer participants. In contrast, 80.7% of observational trials had an anticipated enrollment of 1000 or fewer participants, and 40.7% had 100 or fewer participants. This means that for 40.0% of observational trials, enrollment was within the range of 101–1000 (vs. for 34.2% for interventional trials). The majority of the interventional trials were randomized and non-blind, with prospective cohort trials being the main type of observational trial.

Trial sponsor and funding source

Most trials' lead sponsor was other institutions (78.8% for interventional trials and 80.2% for observational trials), followed by industry (19.1% for interventional trials and 17.4% for observational trials), and the NIH(National Institutes of Health) (1.6% for interventional trials and 2.2% for observational trials) or other US federal agencies (0.5% for interventional trials and 0.2% for observational trials). It should be noted that the data on "lead sponsor" collected in ClinicalTrials.gov represents the primary organization that oversees implementation of the study and may not necessarily represent the source of funding for the study.

Information on different funding sources and trial sites is presented in Table 3 (see table notes for details). Unlike NIH-funded or other trials that were mostly single-site (63.0% for NIH-funded and 82.9% for other), most industry-funded trials were multi-site trials (64.6%). In addition, the industry-funded trials were completed more frequently and were more focused on treatment, whether they were single-site or multi-site trials. In contrast, the NIH-funded and other-funded trials comprised a higher proportion of behavioral and "other" intervention trials. In particular the NIH-funded single-site trials mainly focused on behavioral interventions. With regard to information about trial phase, trials funded by other sponsors have a higher proportion of missing values.

Table 3

Characteristics for Interventional Trials by Funder[a] and Number of Sites, 2008–2019

	Trials, No. (%)					
	Industry-funded		NIH-funded		Other	
	Single-site N = 2786	Multisite N = 5081	Single-site N = 1656	Multisite N = 985	Single-site N = 17734	Multisite N = 3660
Overall status						
Not yet recruiting	51(1.8)	27(0.5)	30(1.8)	12(1.2)	369(2.1)	85(2.3)
Recruiting	316(11.3)	718(14.1)	377(22.8)	204(20.7)	3040(17.1)	902(24.6)
Enrolling by invitation	33(1.2)	57(1.1)	30(1.8)	12(1.2)	239(1.3)	43(1.2)
Active, not Recruiting	148(5.3)	502(9.9)	190(11.5)	169(17.2)	894(5.0)	316(8.6)
Completed	1692(60.7)	3125(61.5)	853(51.5)	499(50.7)	9053(51.0)	1694(46.3)
Suspended	12(0.4)	29(0.6)	19(1.1)	14(1.4)	108(0.6)	23(0.6)
Terminated	191(6.9)	427(8.4)	85(5.1)	43(4.4)	740(4.2)	158(4.3)
Withdrawn	76(2.7)	51(1.0)	30(1.8)	9(0.9)	435(2.5)	43(1.2)
Unknown status	267(9.6)	145(2.9)	42(2.5)	23(2.3)	2856(16.1)	396(10.8)
Primary purpose						
Treatment	1718(61.7)	3867(76.1)	832(50.2)	646(65.6)	9602(55.6)	2096(58.4)
Prevention	458(16.4)	689(13.6)	363(21.9)	191(19.4)	3008(17.4)	617(17.2)
Diagnostic	113(4.1)	80(1.6)	75(4.5)	19(1.9)	996(5.8)	181(5.0)
Other	393(14.1)	325(6.4)	364(22.0)	120(12.5)	3656(21.2)	693(19.3)
Missing	104(3.7)	118(2.3)	23(1.4)	6(0.6)	472(2.7)	73(2.0)
Intervention type						

[a] The trial funding source was determined using the following algorithm: If the lead sponsor was from industry, or the NIH was neither the lead sponsor nor the collaborator and at least one collaborator was from industry, then the study was categorized as “industry funded.” If the lead sponsor was not from industry, and NIH was either the lead sponsor nor the collaborator, then the study was categorized as “NIH-funded.” Otherwise, if the lead sponsor and collaborator fields were not missing, then the study was considered to be funded by “Other.”

	Trials, No. (%)					
Drug	1284(42.1)	3370(66.0)	457(27.8)	476(49.4)	5189(29.3)	1243(34.0)
Behavioral	137(4.5)	40(0.8)	730(44.5)	227(23.6)	3583(20.2)	758(20.7)
Device	468(15.3)	455(8.9)	86(5.2)	56(5.8)	2342(13.2)	386(10.5)
Procedure	95(3.1)	81(1.6)	116(7.1)	79(8.2)	2170(12.2)	349(9.5)
Biological	450(14.7)	1020(20.0)	143(8.7)	130(13.5)	784(4.4)	236(6.4)
Dietary Supplement	172(5.6)	101(2.0)	60(3.7)	20(2.1)	948(5.3)	137(3.7)
Radiation	11(0.4)	20(0.4)	30(1.8)	27(2.8)	218(1.2)	62(1.7)
Genetic	25(0.8)	31(0.6)	10(0.6)	4(0.4)	88(0.5)	44(1.2)
Other	409(13.4)	440(8.6)	381(23.2)	263(27.3)	4426(25.0)	885(24.2)
Enrollment						
1-100	1691(60.9)	2487(49.0)	930(56.2)	427(43.4)	11088(62.8)	1692(47.0)
101–1000	881(31.7)	2208(43.5)	568(34.3)	454(46.1)	5105(28.9)	1491(41.4)
>1000	134(4.8)	330(6.6)	126(7.6)	95(9.6)	1022(5.8)	417(11.6)
Missing	70(2.5)	50(1.0)	30(1.8)	9(0.9)	440(2.5)	42(1.2)
Interventional model						
Single-group	1077(38.7)	1892(37.2)	467(28.2)	275(27.9)	4695(26.5)	888(24.3)
Parallel	1455(52.2)	2820(55.5)	1000(60.4)	630(64.0)	11289(63.7)	2387(65.2)
Crossover	202(7.3)	209(4.1)	96(5.8)	34(3.5)	1154(6.5)	200(5.5)
Factorial	11(0.4)	15(0.3)	54(3.3)	27(2.7)	372(2.1)	93(2.5)
Sequential	29(1.0)	101(2.0)	31(1.9)	18(1.8)	134(0.8)	61(1.7)
Missing	12(0.4)	44(0.9)	8(0.5)	1(0.1)	90(0.5)	31(0.8)
Blinding						
Open	1596(57.6)	2939(58.0)	988(59.7)	606(61.5)	9859(55.9)	2213(60.9)

[a] The trial funding source was determined using the following algorithm: If the lead sponsor was from industry, or the NIH was neither the lead sponsor nor the collaborator and at least one collaborator was from industry, then the study was categorized as “industry funded.” If the lead sponsor was not from industry, and NIH was either the lead sponsor nor the collaborator, then the study was categorized as “NIH-funded.” Otherwise, if the lead sponsor and collaborator fields were not missing, then the study was considered to be funded by “Other.”

	Trials, No. (%)					
Single-blind	236(8.6)	217(4.3)	358(21.6)	117(11.9)	3419(19.4)	613(16.9)
Double-blind	313(11.3)	502(9.9)	105(6.3)	68(6.9)	1728(9.8)	235(6.5)
Triple-blind	208(7.5)	390(7.7)	72(4.3)	67(6.8)	1149(6.5)	224(6.2)
Quadruple-blind	420(15.1)	1017(20.1)	122(7.4)	123(12.5)	1467(8.3)	346(9.5)
Missing	13(0.5)	16(0.3)	11(0.7)	4(0.4)	112(0.6)	29(0.8)
Allocation						
Randomized	1596(57.6)	2758(54.9)	1094(66.1)	647(65.7)	12085(68.6)	2517(69.4)
Nonrandomized	283(10.2)	713 14.2)	164(9.9)	104(10.6)	1766(10.0)	381(10.5)
N/A	889(32.2)	1550(30.8)	385(23.2)	229(23.2)	3756(21.3)	728(20.1)
Missing	18(0.6)	60(1.2)	13(0.8)	5(0.5)	127(0.7)	34(0.9)
Phase						
Early Phase 1	24(0.9)	17(0.3)	34(2.1)	2(0.2)	258(1.5)	18(0.5)
1	289(10.4)	356(7.0)	162(9.8)	118(12.0)	757(4.3)	172(4.7)
1–2	169(6.1)	269(5.3)	102(6.2)	61(6.2)	562(3.2)	138(3.8)
2	456(16.3)	1133(22.4)	234(14.1)	253(25.7)	1474(8.3)	441(12.0)
2–3	66(2.4)	166(3.3)	22(1.3)	21(2.1)	416(2.3)	124(3.4)
3	472(16.9)	1984(38.9)	67(4.0)	144(14.6)	995(5.6)	373(10.2)
4	348(12.4)	498(9.8)	60(3.6)	49(5.0)	1702(9.6)	329(9.0)
N/A	962(34.6)	668(13.0)	975(58.9)	337(34.2)	11570(65.2)	2065(56.4)

[a] The trial funding source was determined using the following algorithm: If the lead sponsor was from industry, or the NIH was neither the lead sponsor nor the collaborator and at least one collaborator was from industry, then the study was categorized as “industry funded.” If the lead sponsor was not from industry, and NIH was either the lead sponsor nor the collaborator, then the study was categorized as “NIH-funded.” Otherwise, if the lead sponsor and collaborator fields were not missing, then the study was considered to be funded by “Other.”

Trial diseases

The top six disease categories for pediatric clinical trials registered on ClinicalTrials.gov were infectious disease (13.1%), cancer (12.8%), immune disease (11.2%), respiratory disease (10.7%), mental disease (8.5%), and digestive diseases (8.1%). Infectious disease accounted for the highest proportion (13.5%) in interventional trials and showed a downward trend. In observational trials, the proportion of cancer trials (14.0%) was highest. **(**Table 4–5**)**

Table 4
Disease categories for Interventional Trials Registered in ClinicalTrials.gov,2008–2019

		Trials, No. (%)				
		All, 2008–2019 (n = 36 136)	2008–2010 (n = 7 029)	2011–2013 (n = 7 486)	2014–2016 (n = 9 883)	2017–2019 (n = 11 738)
Diseases(%)						
Infectious	yes	4863(13.5)	1311(18.7)	1136(15.2)	1166(11.8)	1250(10.6)
	no	31273(86.5)	5718(81.3)	6350(84.8)	8717(88.2)	10488(89.4)
Cancer	yes	4389(12.1)	1025(14.6)	884(11.8)	1136(11.5)	1344(11.4)
	no	31747(87.9)	6004(85.4)	6602(88.2)	8747(88.5)	10394(88.6)
Immune	yes	4288(11.9)	1068(15.2)	934(12.5)	1064(10.8)	1222(10.4)
	no	31848(88.1)	5961(84.8)	6552(87.5)	8819(89.2)	10516(89.6)
Respiratory	yes	3855(10.7)	985(14.0)	918(12.3)	991(10.0)	961(8.2)
	no	32281(89.3)	6044(86.0)	6568(87.7)	8892(90.0)	10777(91.8)
Mental	yes	3544(9.8)	605(8.6)	676(9.0)	971(9.8)	1292(11.0)
	no	32592(90.2)	6424(91.4)	6810(91.0)	8912(90.2)	10446(89.0)
Digestive	yes	2803(7.8)	607(8.6)	631(8.4)	779(7.9)	786(6.7)
	no	33333(92.2)	6422(91.4)	6855(91.6)	9104(92.1)	10952(93.3)

Table 5
Disease categories for Observational Trials Registered in ClinicalTrials.gov,2008–2019

		Trials, No. (%)				
		All, 2008–2019 (n = 16692)	2008–2010 (n = 3116)	2011–2013 (n = 3295)	2014–2016 (n = 4125)	2017–2019 (n = 6156)
Diseases						
Infectious	yes	2061(12.3)	458(14.7)	458(13.9)	469(11.4)	676(11.0)
	no	14631(87.7)	2658(85.3)	2837(86.1)	3656(88.6)	5480(89.0)
Cancer	yes	2343(14.0)	604(19.4)	471(14.3)	493(12.0)	775(12.6)
	no	14349(86.0)	2512(80.6)	2824(85.7)	3632(88.0)	5381(87.4)
Immune	yes	1651(9.9)	399(12.8)	374(11.4)	344(8.3)	534(8.7)
	no	15041(90.1)	2717(87.2)	2921(88.6)	3781(91.7)	5622(91.3)
Respiratory	yes	1807(10.8)	387(12.4)	403(12.2)	395(9.6)	622(10.1)
	no	14885(89.2)	2729(87.6)	2892(87.8)	3730(90.4)	5534(89.9)
Mental	yes	980(5.9)	171(5.5)	179(5.4)	269(6.5)	361(5.9)
	no	15712(94.1)	2945(94.5)	3116(94.6)	3856(93.5)	5795(94.1)
Digestive	yes	1487(8.9)	266(8.5)	288(8.7)	353(8.6)	580(9.4)
	no	15205(91.1)	2850(91.5)	3007(91.3)	3772(91.4)	5576(90.6)

Table 6 shows selected characteristics of all interventional trials registered from January 2008 through December 2019 (n = 36,136), as well as characteristics for infectious disease, cancer, immune disease, and respiratory disease trials compared to all other trials. Cancer trials constituted the largest proportion of trials that were active but not yet recruiting (20.7% vs. 14.0% for immune disease, 11.0% for infectious disease, and 7.0% for respiratory disease). Cancer trials also constituted the largest proportion of trials that were oriented toward treatment (15.0% vs. 14.2% for immune disease, 10.8% for respiratory disease, and 10.3% for infectious disease). In addition, cancer trials accounted for the lowest proportion of completed trials, and most of the trials were in recruitment or other unknown status. At the same time, the infectious disease trials mainly focused on prevention,with medium scale (enrollment between 101 and 1000).While cancer, immune disease, and respiratory disease trials were mainly of small size (with the enrollment between 1 and 100).

Table 6
Trial Characteristics and Summary of Designs for Interventional Trials

	Trials, No. (%)				
	All Trials (N = 36136)	Infectious (n = 4 863)	Cancer (n = 4389)	Immune (n = 4288)	Respiratory (n = 3855)
Overall status					
Not yet recruiting	1253(3.5)	135(2.8)	157(3.6)	119(2.8)	105(2.7)
Recruiting	5557(15.4)	537(11.0)	1182(26.9)	751(17.5)	459(11.9)
Completed	19283(53.4)	3064(63.0)	1480(33.7)	2274(53.0)	2313(60.0)
Suspended	214(0.6)	21(0.4)	35(0.8)	25(0.6)	24(0.6)
Terminated	1751(4.8)	198(4.1)	340(7.7)	238(5.6)	215(5.6)
Withdrawn	977(2.7)	140(2.9)	148(3.4)	134(3.1)	128(3.3)
Active, not Recruiting	2293(6.3)	252(5.2)	475(10.8)	320(7.5)	160(4.2)
Enrolling by invitation	444(1.2)	31(0.6)	40(0.9)	50(1.2)	30(0.8)
Unknown status	4364(12.1)	485(10.0)	532(12.1)	377(8.8)	421(10.9)
Primary purpose					
Treatment	21126(60.0)	2179(45.5)	3167(73.0)	3009(71.6)	2272(60.1)
Prevention	6110(17.4)	1822(38.0)	295(6.8)	472(11.2)	716(18.9)
Supportive Care	1938(5.5)	114(2.4)	347(8.0)	215(5.1)	178(4.7)
Diagnostic	1623(4.6)	221(4.6)	277(6.4)	132(3.1)	210(5.6)
Other	1607(4.6)	118(2.5)	94(2.2)	137(3.3)	115(3.0)
Health Services Research	1460(4.1)	194(4.0)	77(1.8)	112(2.7)	155(4.1)
Basic Science	948(2.7)	96(2.0)	50(1.2)	102(2.4)	95(2.5)
Screening	296(0.8)	43(0.9)	25(0.6)	18(0.4)	33(0.9)
Device Feasibility	92(0.3)	4(0.1)	6(0.1)	6(0.1)	8(0.2)
Missing	936(2.6)	72(1.5)	51(1.2)	85(2.0)	73(1.9)
Enrollment					
1-100	20614(58.9)	1590(33.8)	3037(71.9)	2576(62.1)	1902(51.1)
101–1000	11995(34.2)	2267(48.2)	1063(25.2)	1386(33.4)	1515(40.7)
>1000	2417(6.9)	847(18.0)	126(3.0)	183(4.4)	304(8.2)

	Trials, No. (%)				
Sex, %					
Female only	2469(6.9)	283(5.8)	405(9.3)	84(2.0)	46(1.2)
Male only	1015(2.8)	71(1.5)	206(4.7)	63(1.5)	14(0.4)
Both	32532(90.3)	4501(92.7)	3767(86.0)	4132(96.6)	3787(98.4)
Missing	120(0.3)	8(0.2)	11(0.3)	9(0.2)	8(0.2)
Interventional group					
Single-group	10304(28.7)	1081(22.3)	2421(56.1)	1517(35.6)	856(22.2)
Parallel	22420(62.4)	3506(72.4)	1689(39.1)	2302(54.0)	2586(67.1)
Crossover	2139(6.0)	131(2.7)	94(2.2)	332(7.8)	337(8.7)
Factorial	647(1.8)	83(1.7)	35(0.8)	49(1.1)	40(1.0)
Sequential	407(1.1)	41(0.8)	80(1.9)	63(1.5)	30(0.8)
Missing	219(0.6)	21(0.4)	70(1.6)	25(0.6)	6(0.2)
Blinding					
Open	20426(56.9)	2676(55.3)	3678(84.6)	2755(64.6)	1911(49.6)
Single-blind	5757(16.0)	536(11.1)	280(6.4)	306(7.2)	461(12.0)
Double-blind	3523(9.8)	479(9.9)	171(3.9)	383(9.0)	431(11.2)
Triple-blind	2427(6.8)	386(8.0)	92(2.1)	322(7.5)	368(9.5)
Quadruple-blind	3783(10.5)	765(15.8)	125(2.9)	500(11.7)	671(17.4)
Missing	220(0.6)	21(0.4)	43(1.0)	22(0.5)	13(0.3)
Allocation					
Randomized	23643(66.0)	3511(72.5)	1481(34.3)	2417(56.9)	2810(72.9)
Nonrandomized	3869(10.8)	516(10.7)	742(17.2)	570(13.4)	362(9.4)
N/A	8327(23.2)	816(16.8)	2095(48.5)	1258(29.6)	669(17.4)
Missing	297(0.8)	20(0.4)	71(1.6)	43(1.0)	14(0.4)
Phase					
0	410(1.1)	26(0.5)	97(2.2)	54(1.3)	29(0.8)
1	2043(5.7)	280(5.8)	719(16.4)	383(8.9)	166(4.3)
1/2	1393(3.9)	144(3.0)	420(9.6)	316(7.4)	94(2.4)

	Trials, No. (%)				
2	4312(11.9)	666(13.7)	1116(25.4)	814(19.0)	473(12.3)
2/3	900(2.5)	161(3.3)	119(2.7)	116(2.7)	97(2.5)
3	4525(12.5)	1177(24.2)	406(9.3)	789(18.4)	838(21.7)
4	3438(9.5)	840(17.3)	169(3.9)	440(10.3)	507(13.2)
NA	19115(52.9)	1569(32.3)	1343(30.6)	1376(32.1)	1651(42.8)

Differences in trial design were also evident among disease types. With regard to interventional trials, single-group trials accounted for 56.1% of the total number of cancer trials, which was different from the non-cancer trials focused on the other three diseases. These trials were dominated by parallel intervention groups. Cancer trials were more likely to use interval allocation (48.5% vs. 29.6% for immune disease, 17.4% for respiratory disease, and 16.8% for infectious disease). The majority of cancer trials (84.6%) were not blinded. Infectious disease trials, on the other hand, were more likely to use randomized allocation (72.5% vs. 56.9% for immune disease and 34.3% for cancer)

Infectious and respiratory disease trials were more oriented toward later-phase research (i.e., phases 3 and 4) while cancer and immune disease trials displayed a higher relative proportion of earlier-phase trials (i.e., phases 0 through 2).

Public reporting of clinical trial results

Among the registered trials from 2008 to 2019, 46,935 (88.5%) registered trials did not report trial results, representing 95.7% (15,970/16,692) of the observational trials and 85.0% (30,733/36,136) of the interventional trials. In general, industry-led trials had a higher rate of trial result reporting. In the observational registry, federally-led trials had a relatively high rate of result reporting. The results reporting proportion of industry-led interventional is higher than the results reporting proportion of federally-led trials. In terms of trial size, medium and small-scale trials (with number of participants between 1-100 or 101–1000) have a higher proportion of results reported. As shown in Table 7, the late-stage studies of intervention trials (i.e., phases 3 and 4) had a higher proportion of results reported.

Table 7
Public reporting of pediatric clinical trial results

	Trials, No. (%)					
	All studies		Observational		Interventional	
	Has Results (N = 6125)	No Results Available (N = 46935)	Has Results (N = 722)	No Results Available (N = 15970)	Has Results (N = 5403)	No Results Available (N = 30733)
Lead sponsor						
Industry	3080(30.4)	7053(69.6)	458(15.8)	2441(84.2)	2622(36.9)	4479(63.1)
NIH	132(15.7)	709(84.3)	3(0.8)	365(99.2)	129(27.5)	340(72.5)
US federal	52(20.0)	208(80.0)	7(18.4)	31(81.6)	45(20.5)	175(79.5)
Other	2861(6.8)	38965(93.2)	254(1.9)	13133(98.1)	2607(9.2)	25739(90.8)
Enrollment						
1-100	3349(12.3)	23883(87.7)	218(3.3)	6400(96.7)	3131(15.2)	17483(84.8)
101–1000	2248(12.1)	16259(87.9)	290(4.5)	6222(95.5)	1958(16.3)	10037(83.7)
>1000	528(9.5)	5025(90.5)	214(6.8)	2922(93.2)	314(13.0)	2103(87.0)
Phase						
Early Phase 1	13(3.2)	397(96.8)	-	-	13(3.2)	397(96.8)
Not Applicable	1554(8.1)	17561(91.9)	-	-	1554(8.1)	17561(91.9)
Phase 1	190(9.3)	1853(90.7)	-	-	190(9.3)	1853(90.7)
Phase 1/2	244(17.5)	1149(82.5)	-	-	244(17.5)	1149(82.5)
Phase 2	1069(24.8)	3243(75.2)	-	-	1069(24.8)	3243(75.2)
Phase 2/3	129(14.3)	771(85.7)	-	-	129(14.3)	771(85.7)
Phase 3	1488(32.9)	3037(67.1)	-	-	1488(32.9)	3037(67.1)
Phase 4	716(20.8)	2722(79.2)	-	-	716(20.8)	2722(79.2)

We identified completed studies by using the “primary completion date” field. Figure 1 shows the trend of result reporting over time. The number of results reported from registered trials increased slowly and accounted for a very low proportion of total registry trials. Both NIH regulations and trial reporting policies require sponsors or researchers to submit results data within one year of the primary completion date of the trial. Aiming to systematically assess the compliance with results reporting on ClinicalTrials.gov, we

added the primary completion date to the analysis. After 2015, although the number of completed trials increased significantly, the number of trials with results reported increased very little. If the registered trials completed between 2008 and 2018 are pushed forward by one year (as shown by the dotted line in Fig. 1), the gap between the number of trials with results reported and the number of completed trials will increase year by year from 2016 to 2017. After the trial types are separated, as shown in Fig. 2 and Fig. 3, the proportion of observational trials with results reported was lower than that proportion for interventional trials.

Discussion

This analysis provides a preliminary overview of clinical registration trials in the pediatric field over the past 12 years, and the results of this analysis provide a basis for understanding of the treatment and prevention of childhood diseases in the United States. From this report, there are a few observations that deserve our attention.

First, the clinical registration trials that we're looking at are trials involving children. Compared to characteristics of clinical registration trials that include the whole population [10], clinical registration trials for children are typically small-scale trials that mainly focus on drug interventions. we describe clinical registry trials involving both children and adults, which are often excluded from pediatric reviews. There is data that shows that RCTS (Randomized Controlled Trials) that recruit children or recruit adults at the same time are more likely to complete trials than those that recruit adults only [15]. According to the data results of this study, compared to trials that include children and adults separately, the completion rate and behavioral intervention rate for trials only for children are higher. On the one hand, the data also suggest a higher completion rate for pediatric clinical registration trials, which may result in less waste of human and financial resources [16].

Second, the data also suggest that in addition to drug intervention trials, clinical trials on behavioral intervention in children are also developing and gradually playing an important role in pediatric clinical intervention research. At the same time, we observed an upward trend in the number of behavioral type registered trials among the interventional trial group in pediatric clinical registered trials. Further analysis of the data showed that although the proportion of drug intervention trials was different for all the other disease types except mental, drug intervention trials still comprised the largest proportion of trials, while behavioral interventional trials have also increased. The proportion of behavioral intervention trials in mental diseases was significantly higher than that proportion in other diseases and presented an increase year by year, but there was no significant change after subgroup classification in children. As of 2001, the World Health Organization reported that one in four people worldwide suffer from a mental health disorder during their lifetime, and 46.6 million people in the United States currently suffer from a mental health disorder [17]. The mental health research community has used ClinicalTrials.gov to help answer such questions about its use of ClinicalTrials.org.

Third, while previous studies have mainly focused on interventional trials, we have also included observational trials in the process of our analysis, and the number of observational clinical trials in

children has also increased. Although the registration of randomized trials has been widely accepted, the registration of observational studies remains controversial. For example, studies have shown that registration of observational trials cannot effectively prevent false positive results in observational studies [12]. Some of these studies were registered after their results were published, and post-publication registration is unlikely to have the expected benefits of reducing publication bias or selective analysis and reporting of results, since researchers can selectively register research ideas after the data has been explored [13]. In addition, our study found that the reporting rate for results of registered observational trials was significantly lower than the reporting rate for results of interventional trials. This low reporting rate may partly reflect the longer trial cycle of many observational studies. Previous studies have shown that the full dissemination of research methods and results in a timely and impartial manner is essential for the full realization of research benefits [14]. Therefore, although the registration of observational studies is still controversial, under the background of the registration policy, observational registration trials, especially small and medium-sized prospective cohort trials, still show a significant increase.

Last but not least, we are concerned about the reporting of results for registered trials. Given that policy requires trials to report results, the quality of results reporting of existing pediatric registered trials is still poor and has significant room for improvement. The FDA and the final rule do not mandate that all trials report their results to the registry, which may be the reason that few trials report their results [18] (**eTable**). In addition, the final rule expanded the proportion of trials that must report results to the registry on January 18, 2017, and therefore, after this date, the reporting of results of registered trials may increase. Clinical trials registered before policy implementation were less likely to report results, and the results of our descriptive analysis were consistent with previous analyses using the ClinicalTrials.gov registry [19]. Funding agencies and types of interventions were associated with results reporting. Dissemination of research results is critical to clinical practice and selective reporting can lead to distortion of knowledge in the field. We conducted a preliminary descriptive analysis of the possible factors influencing the reporting of the results for pediatric registered trials and found that, on the whole, the rate of results reporting of the trials led by industry, the major sponsor, were better. Our analysis also confirms what previous studies have shown: industry sponsors tend to be well-staffed and have a centralized process to support the submission of results, while non-industry sponsors tend to rely on a single investigator with very little centralized support [20]. How to improve the quality of results reporting may be an issue to consider in the future. In this optimization process, we also need to consider the entire life cycle of clinical trials.

Several limitations of our study should be noted. First, there are trials that are not registered with ClinicalTrials.gov or any other publicly accessible registry, and these trials are not included in our evaluation. Although ClinicalTrials.gov is one of the largest international trial registries containing 70% of trials registered under the World Health Organization's international clinical trials registry, it is not an exhaustive list of all clinical trials in the United States [20]. Second, not all trials, for example phase I trials or trials looking at non-drug interventions, meet FDA or final rule requirements [21]. There may be other incentives and norms that bias the registration of trials with certain characteristics, and trends identified by registries reflect at least partial changes in trial reporting rather than changes in how trials are conducted or designed. Thirdly, our study focuses on clinical registration trials involving children, and rigorous

analysis of pediatric clinical registration trials may consider dividing child-only registration trials into a separate analysis for comparison. In 2012, a study by Pasquali et al. found that an assessment of the clinical trial site data set could describe the overall mix of clinical trials related to children in the United States, which was previously impossible [22]. Subsequently, descriptive analyses of clinical registration trial characteristics of different pediatric diseases emerged [23] [24] [25]. Fourth, we have only made a preliminary description of observational clinical registered trials. Fifth, our study is only a preliminary description of the current status of clinical trials for children, and further research is needed to analyze the current status and improve the recommendations for registration information so as to provide the public with more transparent and high-quality clinical trial data information for children.

Declarations

Ethics approval and consent to participate: *The analysis of pediatric clinical trials registered in ClinicalTrials.gov was not considered human subject research. No administrative permission was needed to assess the data.*

Consent for publication: *not applicable*

Availability of data and materials: *The datasets generated and analysed during the current study are available in the Clinical Trials.gov website repository, http://clinicaltrials.gov/ .*

Competing interests: *The authors declare that they have no competing interests*

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Figures

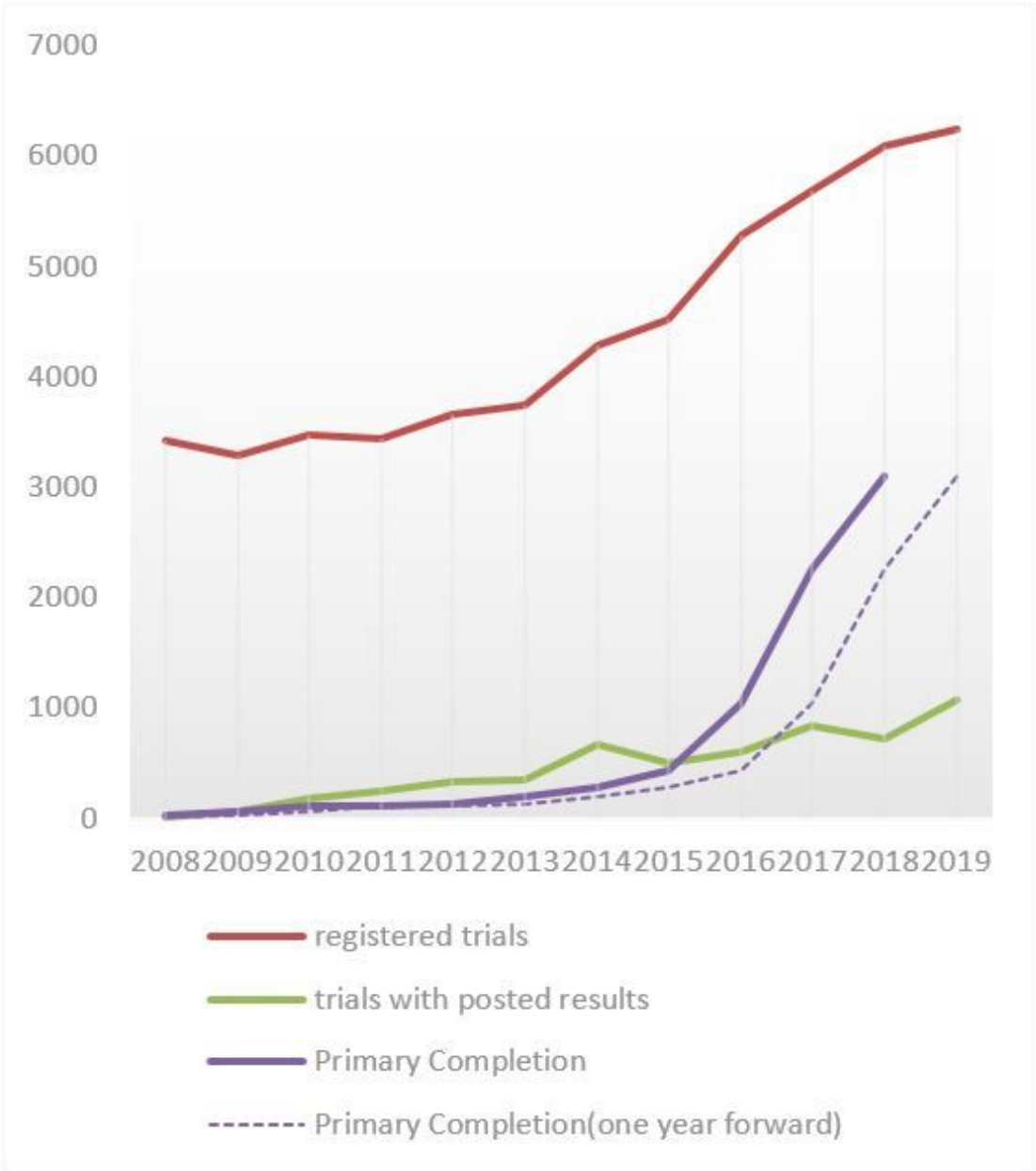

Figure 1

Public reporting completion rate of pediatric clinical trial results

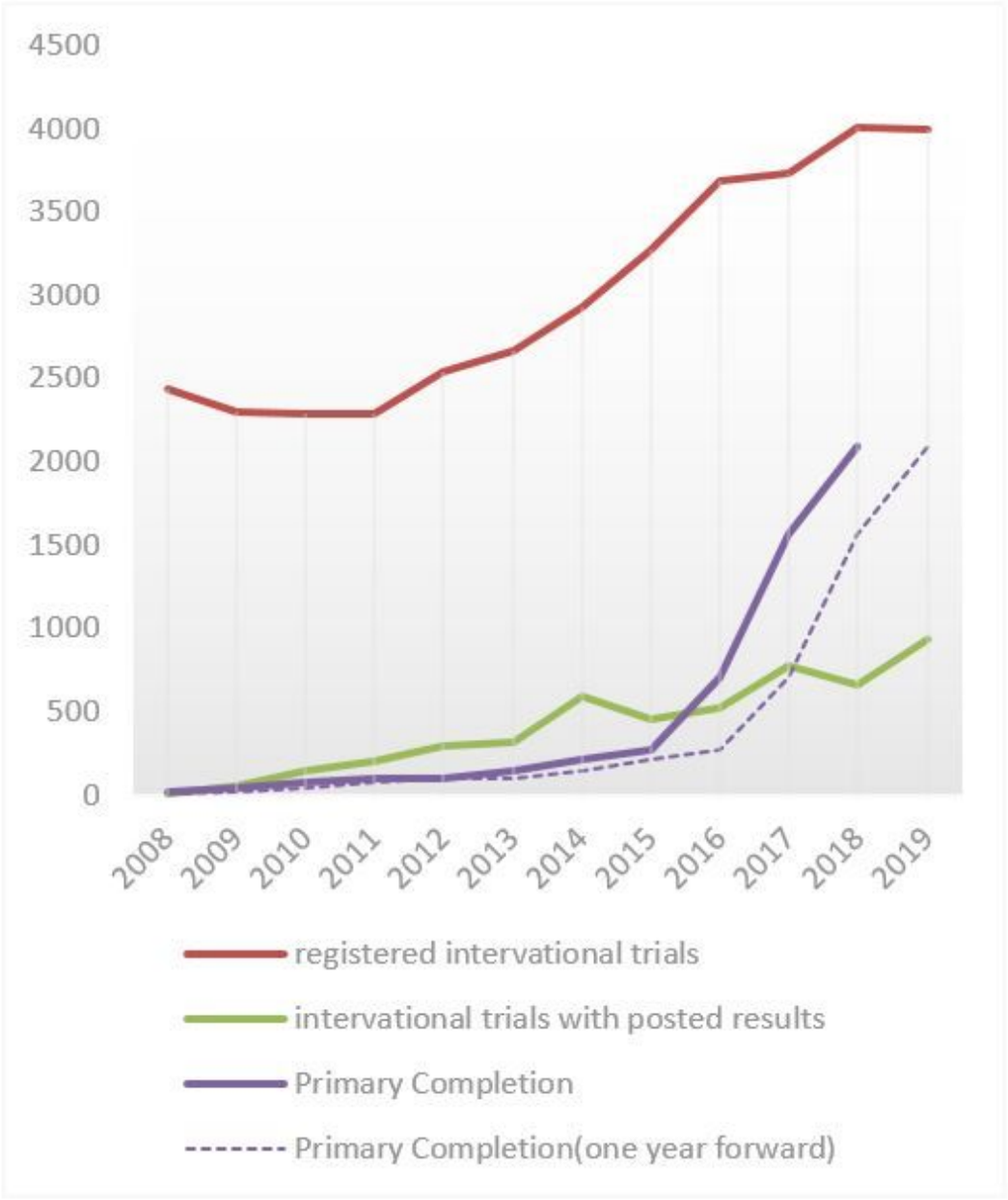

Figure 2

Public reporting completion rate of intervational pediatric clinical trial results

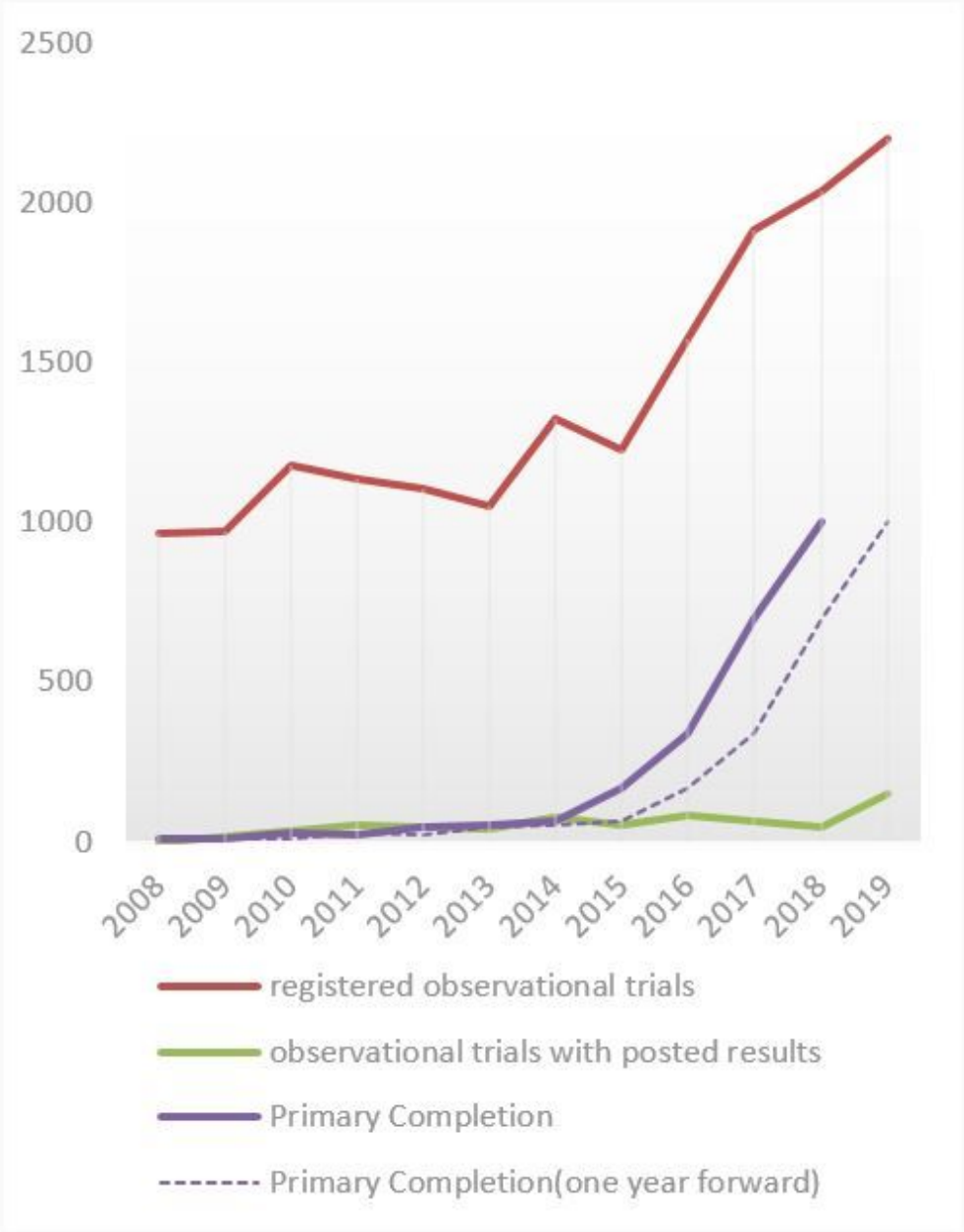

Figure 3

Public reporting completion rate of observational pediatric clinical trial results

Supplementary Files

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- eTable.docx