Status of the Pediatric Clinical Trials Enterprise: An Analysis of the US ClinicalTrials.gov Registry

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KEY WORDS

clinical trials, health policy

ABBREVIATIONS

FDA—Food and Drug Administration

NIH—National Institutes of Health

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WHAT'S KNOWN ON THIS SUBJECT: There are limited data regarding the current status of the pediatric clinical trial enterprise.

WHAT THIS STUDY ADDS: Evaluation of the ClinicalTrials.gov data set allows description of the overall portfolio of clinical trials relevant to US children, which was previously not possible.

abstract

BACKGROUND AND OBJECTIVES: Clinical trials are the gold standard for generating evidence-based knowledge in medicine. Recent legislation requiring trials to be registered at ClinicalTrials.gov has enabled evaluation of the clinical trial enterprise as a whole, which was previously not possible. The purpose of this study was to create a snapshot of the pediatric clinical trial portfolio.

METHODS: All interventional trials registered at ClinicalTrials.gov from July 2005 to September 2010 were included. Pediatric (ie, enrolling patients aged 0–18 years) trial characteristics, therapeutic area, location, and funding were described. Secondary objectives included describing pediatric trials over time and comparison with nonpediatric trials.

RESULTS: During this time, 5035 pediatric trials were registered compared with >10 times as many nonpediatric trials. Neonates/infants were eligible for enrollment in 46.6% of trials versus children (77.9%) and adolescents (45.2%). Nearly one-half of pediatric trials enrolled <100 subjects, and more pediatric trials versus nonpediatric trials evaluated preventive therapies. The proportion of pediatric trials evaluating a drug intervention declined over time, and there were fewer Phase 0 to II versus Phase III to IV trials. Infectious disease/vaccine studies (23%) were the most common, followed by psychiatric/mental health (13%) studies. Many trials enrolled patients outside the United States, and <15% of trials were sponsored by the National Institutes of Health or other US federal agencies.

CONCLUSIONS: Analysis of the ClinicalTrials.gov data set allows description of the current scope of pediatric trials. These data may be useful to stakeholders in informing decisions regarding the conduct of trials in children and provide insight into mechanisms to advance pediatric trial infrastructure and methodology toward improving child health. *Pediatrics* 2012;130:e1269–e1277

Clinical trials are considered the gold standard for evaluating the safety and efficacy of new therapies and generating evidence-based knowledge in medicine. Recently, several questions have been raised regarding the conduct of clinical trials in children, including how best to prioritize and stimulate research in the areas of greatest clinical need, funding and regulatory issues, and the globalization of research.^{1–3} In addition, the general underrepresentation of children in clinical research and the limited pediatric evidence-base has lead to several recent federal initiatives aimed at stimulating research in children, beginning with the Pediatric Exclusivity Provision in 1997.^{4–6} However, it has been difficult to assess the current status of the clinical trial enterprise as a whole, both in terms of characterizing the overall scope of trials being performed and describing changes over time.

The creation of ClinicalTrials.gov in 2000 enabled such analyses to be performed. This registry, mandated by Congress, was intended to assist patients in gaining access to clinical trials and improve transparency. It contains a standard set of information for each trial, and recent initiatives have expanded the number of trials registered and information submitted. Beginning on July 1, 2005, the International Committee of Medical Journal Editors required registration of interventional trials in a public trials registry (such as ClinicalTrials.gov) as a condition for publication.^{7,8} In addition, in 2007, Congress passed legislation (Section 801 of the US Food and Drug Administration [FDA] Amendments Act) expanding the legal requirements to register trials and report key data elements along with basic trial results at ClinicalTrials.gov.⁶

The purpose of the current analysis was to describe the pediatric trial portfolio using ClinicalTrials.gov data,

including trial characteristics, enrollment, study design, therapeutic area, location, and sponsor. Secondary aims included comparing these characteristics between pediatric and nonpediatric trials and describing trends in pediatric trials over time.

METHODS

Data Source

A data set of 96 346 clinical studies registered at ClinicalTrials.gov was downloaded on September 27, 2010. The data set was locked, and a relational database was subsequently designed to facilitate analysis.⁹

Study Selection

All trials entered as a study type of “interventional” registered from July 1, 2005 (the date that the International Committee of Medical Journal Editors guidelines took effect), to September 27, 2010 (the date the database was downloaded), were eligible for inclusion ($N = 68\,134$ studies). ClinicalTrials.gov defines interventional studies as those in which an investigator assigns an intervention based on a protocol.¹⁰ Non-interventional or observational studies were excluded because there are no current requirements regarding their registration at ClinicalTrials.gov. Of the included interventional trials, those enrolling patients aged 0 to 18 years were characterized as pediatric trials ($n = 5035$ studies). These pediatric trials were compared with nonpediatric trials (those restricting enrollment to patients aged ≥ 18 years ($n = 55\,515$)). Of note, studies that did not report age exclusions or potentially enrolled some pediatric patients in addition to adults ($n = 7584$ [11.1%]) were excluded for the purposes of our analysis. We did not limit our analysis to trials conducted solely within the United States. This approach was chosen because our aim was to evaluate the overall portfolio of clinical trials relevant to the use of

medical products in US children. It has been shown previously that many studies affecting the use and labeling of medications marketed in the United States enroll patients in a variety of other countries.²

Data Collection

As previously described, trial data are self-reported by trial sponsors or investigators by using a Web-based system.⁸ Each record contains a set of data elements describing the study's purpose, recruitment/enrollment, design, eligibility criteria, location, sponsor, and other protocol information; standard definitions are used, although not all fields are mandatory.¹⁰ The primary therapeutic area of the pediatric studies was characterized by evaluation of the key words and conditions entered for the study in ClinicalTrials.gov by a single investigator.

Analysis

Trial characteristics were described by using standard summary statistics. Categorical variables were reported as proportions and continuous variables as medians and ranges. Both the pediatric and nonpediatric studies were described. Pediatric studies were also evaluated over the period from July 2005 to September 2007 and October 2007 to September 2010 to describe trends over time. Due to the descriptive nature of the study, formal statistical comparisons were not made.

RESULTS

General Trial Characteristics

From July 1, 2005, to September 27, 2010, a total of 5035 pediatric trials were registered at ClinicalTrials.gov compared with >10 times as many non-pediatric trials ($n = 55\,515$) (Table 1). The average number of pediatric trials registered over time was 80 trials per month from July 2005 to September 2007, and 80 trials per month from

October 2007 to September 2010. With regard to age group, the proportion of trials reporting neonates or infants eligible for enrollment was 46.6% compared with 77.9% enrolling children and 45.2% enrolling adolescents. Other notable trends included the amount of missing data for many of the ClinicalTrials.gov data elements, although this improved for some of the variables during the latter time period. Overall, variables with the most missing data included the field regarding whether the study had a data monitoring committee (33.6% missing) and the type of arms in the trial (eg, experimental, placebo, etc; 30.9% missing). This was generally similar for both the non-pediatric and pediatric trials. In addition, few pediatric and nonpediatric trials reported trial results in ClinicalTrials.gov (4.2% of pediatric trials overall; 2.8% of nonpediatric trials).

Trial Type and Design

A substantial proportion of both pediatric (49%) and nonpediatric (61%) trials were small studies, enrolling <100 subjects (Table 1). The majority of pediatric studies were randomized and included a placebo or comparator arm (Table 2). Overall, 27.2% of pediatric trials evaluated a preventive therapy versus 9.7% of nonpediatric trials. In contrast, 64.0% of pediatric trials evaluated disease treatment compared with 78.6% of nonpediatric trials. Examination of the proportion of pediatric trials evaluating a drug intervention over time showed that 55% of trials occurred in the early time period versus 44% of trials in the latter time period (Table 2). Assessed in another way, the average number of drug intervention trials registered per month in the early time period was 44, compared with 35 trials per month in the latter time period. Examination of trial type according to age showed that among trials enrolling neonates/infants, 47.7% involved a drug intervention, compared with 52.9% of

trials enrolling children and 56.1% of trials enrolling adolescents. In contrast, trials enrolling neonates/infants involved a greater proportion of biologic agent trials (which includes vaccine trials): 22.2% infants/neonates, 13.0% children, and 7.8% adolescents. There were few pediatric pharmacokinetic/pharmacodynamic trials and few Phase 0 to II trials (versus Phase III–IV trials) in either time period. The primary therapeutic area of pediatric trials is displayed in Fig 1. Infectious disease/vaccine studies (23%) were the most common, followed by psychiatric/mental health trials (13%).

Trial Location and Sponsor

Both pediatric and nonpediatric trials included study sites in a number of regions outside the United States (Table 3). Overall, 7.1% of pediatric trials had study sites in Africa versus 2.0% of nonpediatric trials. Most pediatric studies were sponsored by academic institutions/medical centers (48.0% overall), followed by industry (32.3%) and the National Institutes of Health (NIH) or other US federal agencies (7.8%). Among pediatric studies with industry as the lead sponsor, the majority (56.6%) were drug intervention studies. 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. The total proportion of pediatric studies for which the NIH or other US federal agency was listed as a lead or collaborating sponsor was 14.4% overall and 16.9% in the early time period versus 12.5% in the later time period. Federal agencies listed as lead sponsor or collaborator for ≥ 10 of the pediatric studies are displayed in Table 4. The National Institute of Mental Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development were

the most common federal agencies listed, each accounting for >100 pediatric studies.

DISCUSSION

This analysis provides the first snapshot of the landscape of pediatric clinical trials, whose results provide the basis for treatment and prevention of diseases in children in the United States. As this publically available database is updated and improved, it will continue to provide transparency regarding the type, design, distribution, and funding of clinical trials. From this report of clinical trials in children, several noteworthy observations emerge.

First, although children comprise one-quarter of the US population, we observed >10 times as many adult trials registered at ClinicalTrials.gov compared with pediatric trials.¹¹ Although the observation of the underrepresentation of children in clinical research has been made previously, this is the first attempt at quantifying the magnitude of this discrepancy.¹ Regarding the age of children enrolled, we found that neonates/infants were eligible for enrollment in fewer trials (46.6%) compared with older children (77.9%) and adolescents (45.2%). However, these data suggest that the neonate/infant age group is actually well represented when the age distribution of the overall pediatric population is considered (~5% of those aged <18 years are <1 year of age).¹² It is important to note that the data currently collected in ClinicalTrials.gov do not tell us how many patients in various age groups were actually enrolled (only who was eligible for enrollment). Further evaluation of study results entered into ClinicalTrials.gov or published in the literature will be required to analyze this question in more detail.

The relatively lower number of trials in children compared with adults is likely related to a number of factors. Many

TABLE 1 Trial Characteristics

Characteristic	Pediatric <i>n</i> = 5035	Nonpediatric <i>n</i> = 55 515	Pediatric July 2005–September 2007 <i>n</i> = 2153	Pediatric October 2007–September 2010 <i>n</i> = 2882
Year enrollment began/planned to begin				
Before 2005, (%)	1107/4902 (22.6)	9878/54 145 (18.2)	794/2059 (38.6)	313/2843 (11.0)
2005–2011, (%)	3795/4902 (77.4)	44 261/54 145 (81.7)	1265/2059 (61.4)	2530/2843 (89.0)
After 2011, (%)	0/4902 (0.0)	6/54 145 (0.0)	0/2059 (0.0)	0/2843 (0.0)
Missing, (%)	133/5035 (2.6)	1370/55 515 (2.5)	94/2153 (4.4)	39/2882 (1.4)
Study duration, y ^a	1.9 (1.0–3.2)	1.9 (1.0–3.0)	2.7 (1.5–4.0)	1.7 (0.9–2.9)
Missing, (%)	1245/5035 (24.7)	12 514/55 515 (22.5)	1057/2153 (49.1)	188/2882 (6.5)
Overall recruitment status				
Not yet recruiting, (%)	376/5035 (7.5)	3322/55 515 (6.0)	44/2153 (2.0)	332/2882 (11.5)
Recruiting, (%)	1539/5035 (30.6)	18094/55 515 (32.6)	356/2153 (16.5)	1183/2882 (41.0)
Enrolling by invitation, (%)	83/5035 (1.6)	699/55 515 (1.3)	7/2153 (0.3)	76/2882 (2.6)
Active, not recruiting, (%)	644/5035 (12.8)	7873/55 515 (14.2)	310/2153 (14.4)	334/2882 (11.6)
Completed, (%)	2167/5035 (43.0)	21 946/55 515 (39.5)	1318/2153 (61.2)	849/2882 (29.5)
Suspended, (%)	24/5035 (0.5)	370/55 515 (0.7)	6/2153 (0.3)	18/2882 (0.6)
Terminated, (%)	160/5035 (3.2)	2718/55 515 (4.9)	93/2153 (4.3)	67/2882 (2.3)
Withdrawn, (%)	42/5035 (0.8)	493/55 515 (0.9)	19/2153 (0.9)	23/2882 (0.8)
Missing	0	0	0	0
Primary purpose				
Treatment, (%)	3070/4796 (64.0)	40 951/52 086 (78.6)	1351/2066 (65.4)	1719/2730 (63.0)
Prevention, (%)	1306/4796 (27.2)	5030/52 086 (9.7)	605/2066 (29.3)	701/2730 (25.7)
Diagnostic, (%)	122/4796 (2.5)	2046/52 086 (3.9)	50/2066 (2.4)	72/2730 (2.6)
Supportive care, (%)	129/4796 (2.7)	1261/52 086 (2.4)	20/2066 (1.0)	109/2730 (4.0)
Screening, (%)	10/4796 (0.2)	214/52 086 (0.4)	2/2066 (0.1)	8/2730 (0.3)
Health services research, (%)	66/4796 (1.4)	647/52 086 (1.2)	11/2066 (0.5)	55/2730 (2.0)
Basic science, (%)	73/4796 (1.5)	1715/52 086 (3.3)	7/2066 (0.3)	66/2730 (2.4)
Educational/counseling/ training, (%)	20/4796 (0.4)	222/52 086 (0.4)	20/2066 (1.0)	0/2730 (0.0)
Missing, (%)	239/5035 (4.7)	3429/55 515 (6.2)	87/2153 (4.0)	152/2882 (5.3)
End point classification				
Safety, (%)	331/4249 (7.8)	3813/45 556 (8.4)	153/1885 (8.1)	178/2364 (7.5)
Efficacy, (%)	1763/4249 (41.5)	14817/45 556 (32.5)	729/1885 (38.7)	1034/2364 (43.7)
Safety/efficacy, (%)	1900/4249 (44.7)	22 669/45 556 (49.8)	903/1885 (47.9)	997/2364 (42.2)
Bioequivalence, (%)	15/4249 (0.4)	1041/45 556 (2.3)	7/1885 (0.4)	8/2364 (0.3)
Bioavailability, (%)	14/4249 (0.3)	297/45 556 (0.7)	5/1885 (0.3)	9/2364 (0.4)
Pharmacokinetics, (%)	136/4249 (3.2)	1370/45 556 (3.0)	45/1885 (2.4)	91/2364 (3.8)
Pharmacodynamics, (%)	20/4249 (0.5)	727/45 556 (1.6)	9/1885 (0.5)	11/2364 (0.5)
Pharmacokinetics/dynamics, (%)	70/4249 (1.6)	822/45 556 (1.8)	34/1885 (1.8)	36/2364 (1.5)
Missing, (%)	786/5035 (15.6)	9959/55 515 (17.9)	268/2153 (12.4)	518/2882 (18.0)
Enrollment (no. of subjects) ^a				
Median (interquartile range)	104.5 (44.0–298.0)	70 (32.0–200.0)	126 (50.0–340.0)	100 (40.0–250.0)
0–50, (%)	1484/4902 (30.3)	22 191/54 030 (41.1)	538/2059 (26.1)	946/2843 (33.3)
51–100, (%)	948/4902 (19.3)	11066/54 030 (20.5)	378/2059 (18.4)	570/2843 (20.0)
101– 500, (%)	1749/4902 (35.7)	15768/54 030 (29.2)	792/2059 (38.5)	957/2843 (33.7)
501–1000, (%)	327/4902 (6.7)	2968/54 030 (5.5)	160/2059 (7.8)	167/2843 (5.9)
>1000, (%)	394/4902 (8.0)	2037/54 030 (3.8)	191/2059 (9.3)	203/2843 (7.1)
Enrollment missing, (%)	133/5035 (2.6)	1485/55 515 (2.7)	94/2153 (4.4)	39/2882 (1.4)
Gender eligible for enrollment				
Female, (%)	105/5035 (2.1)	5375/55 515 (9.7)	40/2153 (1.9)	65/2882 (2.3)
Male, (%)	74/5035 (1.5)	3057/55 515 (5.5)	26/2153 (1.2)	48/2882 (1.7)
Both, (%)	4856/5035 (96.4)	47 083/55 515 (84.8)	2087/2153 (96.9)	2769/2882 (96.1)
Missing	0	0	0	0
Age range eligible for enrollment ^b				
Neonates, 0–30 d, (%)	1009/5035 (20.0)	NA	413/2153 (19.2)	596/2882 (20.7)
Infants, >30 d–1 y, (%)	1341/5035 (26.6)	NA	613/2153 (28.5)	728/2882 (25.3)
Children, 1–12 y, (%)	3922/5035 (77.9)	NA	1675/2153 (77.8)	2247/2882 (78.0)
Adolescents, 12–18 y, (%)	2278/5035 (45.2)	NA	968/2153 (45.0)	1310/2882 (45.5)
Study has data monitoring committee, (%)	1523/3342 (45.6)	15 259/36 980 (41.3)	441/899 (49.1)	1082/2443 (44.3)
Missing, (%)	1693/5035 (33.6)	18 535/55 515 (33.4)	1254/2153 (58.2)	439/2882 (15.2)

TABLE 1 Continued

Characteristic	Pediatric <i>n</i> = 5035	Nonpediatric <i>n</i> = 55 515	Pediatric July 2005–September 2007 <i>n</i> = 2153	Pediatric October 2007–September 2010 <i>n</i> = 2882
Results of trial reported on ClinicalTrials.gov				
Overall, (%)	209/5035 (4.2)	1579/55 515 (2.8)	133/2153 (6.2)	76/2882 (2.6)
For studies completed in 2009 or before, (%)	197/1828 (10.8)	1516/20 281 (7.5)	122/839 (14.5)	75/989 (7.6)

Values are median (interquartile range). NA, not available.

^a Includes both actual and anticipated duration or enrollment for completed and ongoing studies, respectively.

^b Because >1 response under the designated heading is possible, data presented may sum to >100%.

barriers exist to conducting pediatric research, including the relative rarity of disease, disease heterogeneity, lack of research infrastructure, ethical issues in pediatric research, and difficulty in identifying valid clinical end points.^{2,3,13} This lack of evidence on which to base pediatric therapeutic decisions has led in part to wide variation in treatment and outcomes across centers for many diseases, as well as frequent use of off-label medications in children.^{3,14–16} It may be argued that children are relatively “healthy” compared with adults as a justification for fewer clinical trials in this population. However, previous studies have demonstrated that nearly 80% of hospitalized children receive at least 1 off-label medication, which would indicate that there is a limited pediatric evidence-base specifically for ill children requiring hospitalization.¹⁴

In an attempt to fill this gap, Congress passed the FDA Modernization Act in 1997 (which included the Pediatric Exclusivity Provision), the Best Pharmaceuticals for Children Act (2002), the Pediatric Research Equity Act (2003), and, most recently, the FDA Amendments Act (2007).^{4–6,17,18} These initiatives aimed to stimulate research in children, including study of drug dosing, safety, and efficacy, in part through providing financial incentives to pharmaceutical companies.⁴ Although these initiatives have resulted in >400 labeling changes to date, it is interesting to note in our analysis that the proportion of studies evaluating a

drug intervention actually seems to have decreased over time.¹⁹ Furthermore, there were relatively few pediatric pharmacokinetic/pharmacodynamics trials or Phase 0 to II studies conducted during either time period despite the lack of this basic information regarding many pediatric drugs. It may be that many of the drug studies performed under these incentives, particularly of “blockbuster” drugs, were initiated before 2005.²⁰ In addition, this report suggests that the proportion of industry-sponsored pediatric trials seems to have decreased over time, although industry continues to sponsor several times the number of trials as the NIH and other federal agencies even in the recent era. In attempt to bridge many of these gaps, an initiative known as the Pediatric Trials Network was recently funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.²¹ This network creates an infrastructure for conducting pediatric clinical trials spanning a variety of therapeutic areas, including older drugs and devices with expired patents that were not studied under previous initiatives.

Second, this analysis suggests that many of the trials conducted in both the pediatric and adult population are relatively small studies enrolling <100 subjects. Although small trials are necessary in some cases (eg, early-phase drug studies, trials of rare/orphan diseases), obtaining clinically meaningful and generalizable information from small studies

is often challenging. Our data suggest that in the pediatric population, this is not due to a greater proportion of early-phase trials being conducted because there were actually more Phase III to IV trials compared with Phase 0 to II trials. Although there may be a lower cost associated with small individual trials, it is possible that if resources were instead directed toward large trials aimed at answering the most important questions, more useful evidence could be generated without increasing total costs.^{1–3}

Third, it is noteworthy that the distribution of trials with regard to therapeutic area seems to generally mirror overall disease burden in children, and there is a higher percentage of trials focused on disease prevention in children. There have been concerns that trials in children may not reflect disease burden because of financial incentives in place for the pharmaceutical industry in the Pediatric Exclusivity Provision to study drugs with a large adult market.²² Although many pediatric diseases are often acute and self-limiting (otitis media, respiratory tract infections, and gastrointestinal illnesses), many children suffer from chronic diseases such as asthma, obesity, and related sequelae, as well as developmental disorders such as attention-deficit/hyperactivity disorder and autism.²³ Data from the current study suggest that the disease burden overall in children seems to be adequately represented, including infectious disease,

TABLE 2 Trial Type and Design

Characteristic	Pediatric <i>n</i> = 5035 (%)	Nonpediatric <i>n</i> = 55 515 (%)	Pediatric July 2005–September 2007 <i>n</i> = 2153 (%)	Pediatric October 2007–September 2010 <i>n</i> = 2882 (%)
Intervention type ^a				
Drug	2451/5035 (48.7)	36 536/55 515 (65.8)	1184/2153 (55.0)	1267/2882 (44.0)
Procedure	381/5035 (7.6)	6063/55 515 (10.9)	203/2153 (9.4)	178/2882 (6.2)
Biological	774/5035 (15.4)	3409/55 515 (6.1)	394/2153 (18.3)	380/2882 (13.2)
Behavioral	791/5035 (15.7)	4338/55 515 (7.8)	328/2153 (15.2)	463/2882 (16.1)
Device	284/5035 (5.6)	4899/55 515 (8.8)	108/2153 (5.0)	176/2882 (6.1)
Radiation	29/5035 (0.6)	1059/55 515 (1.9)	21/2153 (1.0)	8/2882 (0.3)
Dietary supplement	268/5035 (5.3)	1494/55 515 (2.7)	38/2153 (1.8)	230/2882 (8.0)
Genetic	18/5035 (0.4)	526/55 515 (0.9)	3/2153 (0.1)	15/2882 (0.5)
Other	544/5035 (10.8)	5066/55 515 (9.1)	75/2153 (3.5)	469/2882 (16.3)
Missing	0	0	0	0
Phase				
0	32/5035 (0.6)	303/55 515 (0.5)	3/2153 (0.1)	29/2882 (1.0)
I	339/5035 (6.7)	7887/55 515 (14.2)	136/2153 (6.3)	203/2882 (7.0)
I–II	207/5035 (4.1)	2829/55 515 (5.1)	81/2153 (3.8)	126/2882 (4.4)
II	771/5035 (15.3)	12 806/55 515 (23.1)	330/2153 (15.3)	441/2882 (15.3)
II–III	177/5035 (3.5)	1476/55 515 (2.7)	67/2153 (3.1)	110/2882 (3.8)
III	1276/5035 (25.3)	9631/55 515 (17.3)	709/2153 (32.9)	567/2882 (19.7)
IV	783/5035 (15.6)	7950/55 515 (14.3)	360/2153 (16.7)	423/2882 (14.7)
NA	1450/5035 (28.8)	12 633/55 515 (22.8)	467/2153 (21.7)	983/2882 (34.1)
Missing	0	0	0	0
Allocation				
Randomized	3720/4927 (75.5)	36 914/53 111 (69.5)	1625/2105 (77.2)	2095/2822 (74.2)
Nonrandomized	1207/4927 (24.5%)	16 197/53 111 (30.5)	480/2105 (22.8)	727/2822 (25.8)
Missing	108/5035 (2.1)	2404/55 515 (4.3)	48/2153 (2.2)	60/2882 (2.1)
No. of arms				
1	1059/3930 (26.9)	15 091/44 193 (34.1)	345/1137 (30.3)	714/2793 (25.6)
2	2096/3930 (53.3)	20 920/44 193 (47.3)	567/1137 (49.9)	1529/2793 (54.7)
≥3	775/3930 (19.7)	8182/44 193 (18.5)	225/1137 (19.8)	550/2793 (19.7)
0/missing	1105/5035 (21.9)	11 322/55 515 (20.4)	1016/2153 (47.2)	89/2882 (3.1)
Type of arms ^a				
Experimental	2638/3478 (75.8)	28 257/37 187 (76.0)	663/863 (76.8)	1975/2615 (75.5)
Comparator	1558/3478 (44.8)	15 795/37 187 (42.5)	404/863 (46.8)	1154/2615 (44.1)
Placebo comparator	816/3478 (23.5)	9954/37 187 (26.8)	208/863 (24.1)	608/2615 (23.3)
Sham comparator	43/3478 (1.2)	519/37 187 (1.4)	7/863 (0.8)	36/2615 (1.4)
No intervention	419/3478 (12.0)	2835/37 187 (7.6)	88/863 (10.2)	331/2615 (12.7)
Other type	222/3478 (6.4)	2087/37 187 (5.6)	50/863 (5.8)	172/2615 (6.6)
Missing	1557/5035 (30.9)	18 328/55 515 (33.0)	1290/2153 (59.9)	267/2882 (9.3)

NA, not available.

^a Because >1 response under the designated heading is possible, data presented may sum to >100%.

vaccines, pulmonary diseases, psychiatric/mental health disorders, and endocrine disorders. Further study focusing on the distribution of disease burden within particular therapeutic areas is necessary. In addition, mechanisms for evaluation of longer-term outcomes, particularly safety-related outcomes that may be affected by the dynamic processes of growth and development, are needed because most of the current trials are of relatively short duration.²⁴ Finally, our data support earlier reports demonstrating the globalization of clinical trials.^{2,25} We have shown

previously that 65% of studies conducted under the Pediatric Exclusivity Provision enrolled patients in at least 1 country outside the United States.² In the current analysis, pediatric trials were more commonly conducted in developing nations, such as those in Africa, compared with adult trials. Several possible reasons for the globalization trend have been examined, including: (1) lower labor and infrastructure costs; (2) the availability of a larger pool of research subjects, which reduces trial and drug development time lines; and (3) fewer and less

time-consuming regulatory requirements.^{2,25} Scientific advantages of globalization include potential clinical innovation, as well as evaluation of the safety and efficacy of therapies in more diverse populations, which might lead to a broader impact on global health. In addition, certain therapies may be more appropriately studied in developing countries where there is a higher burden of disease. However, several concerns have also been raised regarding globalization, including the scientific validity of extrapolating results from other patient populations (due to

FIGURE 1

Therapeutic area of pediatric trials. CNS, central nervous system; GI, gastrointestinal; ID, infectious disease.

differences in baseline event rates, background therapy, access to health care resources, and genetic differences) and ethical concerns regarding consent and the availability of health resources and therapy once the trial has ended. These and other issues will need to be further explored and evaluated as the globalization of trials continues.

To the best of our knowledge, this analysis represents the most complete look at the pediatric clinical trials enterprise to date. However, there are several limitations that should be noted. First, the data presented in this study focus on interventional trials because federal requirements do not extend to other types of studies. Second, it is

evident that there is a significant amount of missing or unsubmitted data for certain data fields, which limits the comprehensiveness of analyses that can be performed with these data. Initiatives to support enhancing the completeness of data entered into the database should be considered. These initiatives could include requiring not

TABLE 3 Trial Region and Sponsor

Characteristic	Pediatric <i>n</i> = 5035 (%)	Nonpediatric <i>n</i> = 55 515 (%)	Pediatric July 2005–September 2007 <i>n</i> = 2153 (%)	Pediatric October 2007–September 2010 <i>n</i> = 2882 (%)
Region^a				
Africa	322/4552 (7.1)	1034/50 575 (2.0)	168/1940 (8.7)	154/2612 (5.9)
Central America	94/4552 (2.1)	649/50 575 (1.3)	52/1940 (2.7)	42/2612 (1.6)
East Asia	213/4552 (4.7)	4514/50 575 (8.9)	78/1940 (4.0)	135/2612 (5.2)
Europe	1079/4552 (23.7)	16 309/50 575 (32.2)	502/1940 (25.9)	577/2612 (22.1)
Middle East	211/4552 (4.6)	2045/50 575 (4.0)	81/1940 (4.2)	130/2612 (5.0)
North America	2624/4552 (57.6)	29 746/50 575 (58.8)	1087/1940 (56.0)	1537/2612 (58.8)
North Asia	81/4552 (1.8)	1253/50 575 (2.5)	38/1940 (2.0)	43/2612 (1.6)
Pacifica	105/4552 (2.3)	1856/50 575 (3.7)	53/1940 (2.7)	52/2612 (2.0)
South America	216/4552 (4.7)	1903/50 575 (3.8)	67/1940 (3.5)	149/2612 (5.7)
South Asia	185/4552 (4.1)	1025/50 575 (2.0)	85/1940 (4.4)	100/2612 (3.8)
Southeast Asia	143/4552 (3.1)	1086/50 575 (2.1)	70/1940 (3.6)	73/2612 (2.8)
Missing	483/5035 (9.6)	4940/55 515 (8.9)	213/2153 (9.9)	270/2882 (9.4)
Lead sponsor^b				
Industry	1628/5035 (32.3)	21 774/55 515 (39.2)	767/2153 (35.6)	861/2882 (29.9)
NIH	346/5035 (6.9)	1968/55 515 (3.5)	208/2153 (9.7)	138/2882 (4.8)
US federal (non-NIH)	46/5035 (0.9)	901/55 515 (1.6)	33/2153 (1.5)	13/2882 (0.5)
Other ^c	3015/5035 (59.9)	30 872/55 515 (55.6)	1145/2153 (53.2)	1870/2882 (64.9)

^a Because >1 response under the designated heading is possible, data presented may sum to >100%.

^b Of note, the lead sponsor in ClinicalTrials.gov is the primary organization that oversees implementation of the study. The lead sponsor may not necessarily be the source of funding for the study.

^c For the pediatric trials, further manual classification of the "other" lead sponsor group found that this group was primarily composed of academic institutions/medical centers (*n* = 2418), such that this group accounted for 48.0% (2418 of 5035) of lead sponsorship for the pediatric trials overall.

TABLE 4 Federal Agencies Listed as Primary or Collaborating Sponsor for ≥ 10 Pediatric Studies

Federal Agency	No. of Pediatric Studies
National Institute of Mental Health	135
Eunice Kennedy Shriver National Institute of Child Health and Human Development	125
National Heart, Lung, and Blood Institute	62
National Institute of Allergy and Infectious Diseases	54
National Institute of Diabetes and Digestive and Kidney Diseases	53
Centers for Disease Control and Prevention	48
National Cancer Institute	47
National Center for Research Resources	25
National Eye Institute	22
National Institute on Drug Abuse	19
National Institute of Neurological Disorders and Stroke	17
US Agency for International Development	15
National Institute on Alcohol Abuse and Alcoholism	13
National Institute of Nursing Research	12

only registration of the trial at ClinicalTrials.gov as a condition for publication but requiring that a standard set of data fields be completed. Currently,

few trials report their results in ClinicalTrials.gov. In addition, the proportion of trials entered into ClinicalTrials.gov whose results are subsequently published in the peer-reviewed literature is not known and requires further study. It has previously been shown that less than one-half of the pediatric studies submitted to the FDA for the Pediatric Exclusivity Provision were subsequently published.²⁶ More complete reporting will facilitate further analyses and foster greater transparency. Differences in reporting requirements could affect analyses of trends over time; however, we did observe a similar number of pediatric trials registered during both time periods in this study. Third, no standard or comprehensive classification scheme is used for pediatric disease type or therapeutic area, such that we characterized this factor through manual evaluation of the key words and conditions entered for the study. More standard data entry and definitions regarding this variable and others would facilitate future analyses of these data. Finally, we did not include studies in this analysis that did not report any information regarding age criteria for enrollment or may have enrolled some pediatric patients in addition to adults, as the primary focus was on pediatric trials.

In addition, there are undoubtedly some trials that are not registered in ClinicalTrials.gov or any other publicly accessible registry, and these studies were thus not included in our evaluation. In particular, current federal guidelines do not require registration of Phase I trials, trials not involving a drug or device, and trials not under US jurisdiction.

CONCLUSIONS

Analysis of the ClinicalTrials.gov data set allows description of the current scope of pediatric trials. These data and additional analyses specific to certain diseases or therapeutic area may be useful to stakeholders, including policy makers, academic centers, industry, and investigators, in informing future decisions regarding the conduct of trials in children. Strategies to decrease the amount of missing data, standardize the definition of certain variables, particularly those pertaining to pediatric disease, and improve the completeness of study results entered into ClinicalTrials.gov will facilitate future analyses, which may provide further insight into mechanisms to advance pediatric clinical trial infrastructure and methodology and improve child health.

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