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Reporting of data monitoring committees and adverse events in paediatric trials: a descriptive analysis

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ABSTRACT

Objectives For 300 paediatric trials, we evaluated the reporting of: a data monitoring committee (DMC); interim analyses, stopping rules and early stopping; and adverse events and harm-related endpoints.

Methods For this cross-sectional evaluation, we randomly selected 300 paediatric trials published in 2012 from the Cochrane Central Register of Controlled Trials. We collected data on the reporting of a DMC; interim analyses, stopping rules and early stopping; and adverse events and harm-related endpoints. We reported the findings descriptively and stratified by trial characteristics.

Results Eighty-five (28%) of the trials investigated drugs, and 18% (n=55/300) reported a DMC. The reporting of a DMC was more common among multicentre than single centre trials (n=41/132, 31% vs n=14/139, 10%, p<0.001) and industry-sponsored trials compared with those sponsored by other sources (n=16/50, 32% vs n=39/250, 16%, p=0.009). Trials that reported a DMC enrolled more participants than those that did not (median [range]): 224 (10–60480) vs 91 (10–9528) (p<0.001). Only 25% of these trials reported interim analyses, and 42% reported stopping rules. Less than half (n=143/300, 48%) of trials reported on adverse events, and 72% (n=215/300) reported on harm-related endpoints. Trials that reported a DMC compared with those that did not were more likely to report adverse events (n=43/55, 78% vs 100/245, 41%, p<0.001) and harm-related endpoints (n=52/55, 95% vs. 163/245, 67%, p<0.001). Only 32% of drug trials reported a DMC; 18% and 19% did not report on adverse events or harm-related endpoints, respectively.

Conclusions The reporting of a DMC was infrequent, even among drug trials. Few trials reported stopping rules or interim analyses. Reporting of adverse events and harm-related endpoints was suboptimal.

What is already known on this topic?

- Data monitoring committees aim to safeguard participants and ensure rigorous conduct in trials. They are recommended for trials that recruit from vulnerable populations, including children.
- Reviews of trials published from 1996 to 2002 and 2005 to 2007 showed that the reporting of data monitoring committees was infrequent in paediatric trials.
- Despite not always requiring an independent data monitoring committee, the monitoring of safety data is always warranted in paediatric trials.

What this study hopes to add?

- In a randomly selected sample of 300 paediatric trials published in 2012, 18% reported a data monitoring committee.
- Fifty-two per cent of trials did not report any adverse events data.
- Only 32% of drug trials reported a data monitoring committee; 18% and 19% did not report on adverse events or harm-related endpoints, respectively.

INTRODUCTION

Data monitoring committees (DMCs) help to ensure ethical conduct and participant safety in trials via frequent risk–benefit appraisals to identify 'definitive evidence of benefit, convincing evidence of harm, or sufficient evidence of no potential benefit'.[1] These periodic appraisals (ie, interim analyses) are used to inform recommendations regarding trial modification, continuation or termination (ie, early stopping) based on pre-established stopping rules.[2–4] In order to provide credible and unbiased monitoring of ongoing trials, members of the DMC must be independent of the trial sponsor and typically include a statistician and a clinical expert in the therapeutic area being investigated.[5] In trials that investigate high-risk interventions and/or that recruit from vulnerable populations, the inclusion of bioethicists and patient or parent advocates should also be considered.[5]

Although safety and efficacy data should be monitored in all trials, formal establishment of a DMC might not be needed in trials where the intervention(s) are known to cause minimal risk, or trials of behavioural

interventions or that analyse administrative data.[6] For other trials, deciding whether a DMC is required should be based on the level of safety concern (eg, unknown risks or known risks), the practicality of having a DMC and whether having a DMC would help ensure the scientific validity of the trial.[6] DMCs are always required for trials that evaluate new drugs, biologicals or devices. In those that recruit from vulnerable populations, their establishment should be strongly considered.[2 3]

As children are typically considered to be vulnerable individuals, DMCs are frequently warranted in paediatric trials; however, earlier reviews showed that DMCs were seldom reported.[7–9] Moreover, reviews of trials investigating treatments for common paediatric conditions have found their reporting of harms to be suboptimal, limiting their utility for clinical decision making.[10 11] In an evaluation of a random sample of 300 paediatric trials published in 2007, at which time only limited evidence-based guidance was available for paediatric trials, just 5% reported a DMC and 43% reported adverse events data.[9] Since that time, Standards for Research in (StaR) Child Health published six evidence-based standards addressing priority issues regarding the conduct and reporting of paediatric trials, including guidance on the establishment of DMCs.[12–18]

As the use of DMCs in trials continues to evolve, and in light of the newly published guidance for the conduct and reporting of paediatric trials, we evaluated a sample of paediatric trials published in 2012 to determine the reporting of three distinct but related issues: (A) a DMC, its members and their responsibilities; (B) interim analyses, stopping rules and early stopping; and (C) adverse events and harm-related endpoints.

METHODS

Context

Our methods have been detailed in previous reports.[19 20] A brief description follows.

Sample selection

In November 2013, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) for trials published in 2012.[19 20] CENTRAL is a comprehensive database of reports of randomised and quasirandomised trials, taken mainly from MEDLINE and Embase.[21] As this project was part of an ongoing surveillance initiative,[19] the 2012 publication date was chosen because it was 5 years following an earlier evaluation of a random sample of 300 paediatric trials undertaken in 2007.[9] The date also coincided with the publication of the StaR Child Health Standards, allowing for the establishment of baseline data for the reporting of priority items outlined within each.

We randomly ordered the 2296 unique records retrieved by the search using a computer-generated list in Excel (V.2016, Microsoft Corporation, Redmond, Washington, USA). Next, a single researcher screened the records by title and abstract and selected the first 300 (13%) trials that reported on outcomes for participants aged 0–18 years or that recruited both children and adults with an upper age limit of 21 years. The sample size was selected based on our previous evaluation of trials published in 2007.[9] We did not restrict the sample by language, condition, intervention or outcome type.

Data extraction

We extracted data from each trial using a standard form in Research Electronic Data Capture[22] pertaining to the reporting of: the presence of a DMC (yes or no), its members (defined by their professional role, eg, statistician and healthcare provider) and their responsibilities (eg, adjustments to enrolment and reviewing safety data); interim analyses (yes or no), stopping rules (yes or no) and early stopping (yes or no, and reasons); and the monitoring for and occurrence of adverse events (yes or no, and type) and harm-related endpoints (yes or no, and type).

As part of the larger study, we collected data on characteristics of the publication, trial design, intervention, trial conduct, trial sample, consent and recruitment, outcomes, conclusions, trial registration and risk of bias.[19, 20] Our data extraction guide was modelled after that used in the 2007 study,[9] with new items added following consultation with clinical and methodological experts. The complete data extraction guide is available in a previous report,[19] whereas that for the variables presented in this study is in online supplementary appendix 1. We classified the primary diagnostic category for each trial following the WHO's International Statistical Classification of Diseases and Related Health Problems 10th Revision.[23] Table 1 shows our classification scheme for other relevant trial characteristics. Data related to consent and recruitment, study design, trial registration and risk of bias have been reported elsewhere.[19 20]

We used trial registers, published protocols and/or companion articles to complement data extraction when available. When a registration record was not cited in the publication, we searched the International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), ISRCTN Registry (http://www.isrctn.com/) and Google (http://www.google.ca/). We located registration records for 46% (n=138/300) of the trials.[19] We used protocols and companion articles only when they were cited in the published reports. All data were extracted from the published trials by one researcher and verified by another (AG or MPD) to identify and correct errors or omissions.

Analyses

We analysed the data descriptively in SPSS Statistics (V.25, IBM Corporation, Armonk, New York, USA). We investigated differences in reporting of DMCs, adverse events and harm-related endpoints by trial characteristics using the Fisher's exact test and by sample size using the Mann-Whitney test in StatXact (V.10.0, Cytel, Cambridge, Maryland, USA).

Table 1 Data extraction classification scheme

Classification	Definition
Reasons for early stopping	
(A) Benefit	Stopped because of benefit seen in the intervention group(s).
(B) Harm	Stopped because of harm seen in the intervention group(s).
(C) Futility	Stopped because continuing the trial would be futile relative to establishing a treatment benefit.
(E) Funding	Stopped because funding was for a specific timeframe or limited.
(E) Recruitment	Stopped because of lower than anticipated recruitment.
Reported adverse events	
(A) Severe harms	Serious adverse events, for example, death, hospitalisation, life-threatening outcome, disability or permanent damage.
(B) Any harm	Described non-specifically as 'side effects' or 'any/total/overall adverse events'.
(C) Organ system level harms	Described non-specifically as adverse events in the organ systems, for example, cardiovascular adverse events and gastrointestinal adverse events.
(D) Specific harms	Described specifically, for example, nausea, headache and vomiting.
Reported harm-related endpoints	
(A) Discontinuations due to adverse events	Participants discontinued the trial due to adverse events.
(B) Unexplained withdrawals	Participants withdrew from the trial, but the reason is not reported or reportedly unknown (could be due to adverse events or lack of efficacy).
(C) Mortality	Death from any cause (could be disease progression, adverse events or lack of efficacy).
Primary outcome category	
(A) Behavioural	For example, attitudes and eating behaviours.
(B) Biomarker	For example, blood glucose and urine cultures.
(C) Pain	For example, pain relief and pain prevention.
(D) Physiological	For example, disease progression and mortality.
(E) Psychological	For example, depression assessment scores and neuropsychological test.
(F) Techniques/training	For example, method of intubation and effectiveness of a focus group.
(G) Quality of life	For example, Short Form Health Survey (SF-36), patient satisfaction.
(H) Other	Any outcome that does not fit in another category.

Patient and public involvement

Patients and the public were not directly involved in any aspect of this research.

RESULTS

Trial characteristics

The characteristics of the 300 trials have been reported[19] and are provided for context. Most (n=242/300, 81%) trials used a parallel design and were efficacy or superiority trials (n=279/300, 93%). Thirty-three (11%) were described as pilot or exploratory. The most common funding source was government funding (n=135/300, 45%), followed by private (n=81/300, 27%), academic (n=71/300, 24%), pharmaceutical (n=41/300, 14%) and industry funding (n=9/300, 3%). The most common treatments investigated included drugs (n=85/300, 28%), communication, organisational or educational programmes (n=52/300, 17%), rehabilitation or psychosocial interventions (n=30/300, 10%) and medical devices (n=29/300, 10%). Nearly half (n=140/300, 47%) of the trials were undertaken at a single centre. The most common diagnostic categories included mental and behavioural disorders (n=50/300, 17%), infectious and parasitic diseases (n=39/300, 13%), conditions of the respiratory system (n=30/300, 10%) and conditions originating during the perinatal period (n=28/300, 9%). The trials reported data for the following categories of primary outcomes: behavioural (n=46/300, 15%); biomarker (n=55/300, 18%); pain (n=14/300, 5%); physiological (n=130/300, 43%); psychological (n=28/300, 9%); techniques/training (n=13/300, 4%); and quality of life (n=5/300, 2%). Nine (3%) trials investigated primary outcomes that did not fit into any of these categories, for example, knowledge and healthcare costs.

Data monitoring committees

About one-fifth (n=55/300, 18%) of trials reported a DMC (table 2). Among these, just 20% (n=11/55) reported on its composition. Membership most commonly included physicians (n=9/11, 82%) and statisticians (n=6/11, 55%). No trial (n=0/11) reported the membership of a patient or consumer or community advocate. Sixty percent (n=33/55) of trials that reported a DMC also reported the responsibilities to which it was assigned. Among these, the most common were reviewing safety data (n=26/33, 79%), adjusting enrolment (n=7/33, 21%), and making recommendations regarding trial termination (n=6/33, 18%) and trial conduct (n=6/33, 18%).

Reporting of a DMC was more common among multicentre than single centre trials (n=41/132, 31% vs n=14/139, 10%; p<0.001) (table 3). Trials that reported a DMC randomised larger numbers of participants than those that did not (median [range]: 224 (10–60480) vs 91 (10–9528); p<0.001). Reporting a DMC was more common among trials that tested drugs (n=27/85, 32%), vaccines (n=5/14, 36%), alternative therapeutic interventions (n=4/14, 29%) and prevention or screening interventions (n=3/14, 21%) compared with those that tested communication, organisational or educational programmes (n=4/52, 8%), medical devices (n=2/29, 7%) and rehabilitation or psychosocial interventions (n=1/30, 3%) (p=0.001). None (n=0/9) of the trials that tested surgeries or radiotherapy reported a DMC. Reporting of a DMC did not differ by primary outcome type (p=0.16). Trials with an industry or pharmaceutical sponsor were more likely than those with other forms of sponsorship to report a DMC (n=16/50, 32% vs n=39/250, 16%) (p=0.009).

Table 2 Reporting of DMCs, interim analyses, stopping rules and early stopping

Trial characteristic	N total	N (%)
DMCs		
Reported	300	55 (18)
Not reported		245 (82)
DMC members*		
Physician	55	9 (16)
Statistician		6 (11)
Clinical trial methodologist		1 (2)
Clinical pharmacologist		3 (5)
Bioethicist		1 (2)
Other		3 (5)
Not specified		44 (80)
DMC responsibilities†		
Adjustment to enrolment	55	7 (13)
Make recommendations regarding termination		6 (11)
Review or approve the protocol		3 (6)
Review or make recommendations about trial conduct		6 (11)
Release interim data		1 (2)
Review or approve manuscripts or reports		2 (4)
Review safety data		26 (47)
Other‡		4 (7)
Not reported		22 (40)
Reported on interim analyses		
Yes	55	14 (25)
No		41 (75)
Reported on stopping rules		
Yes	55	12 (22)
No		43 (78)
Reported that the trial stopped early		
Yes	300	13 (4)
For benefit		2/13 (15)
For harm		0/13 (0)
For futility		5/13 (38)
Due to funding limitation		1/13 (8)
Due to inadequate recruitment		5/13 (38)
No		287 (96)

*Nine of the 11 trials (82%) that reported on membership in the DMCs reported more than one type of member.
†13 of the 33 trials (39%) that reported on the DMC's responsibilities reported more than one responsibility.
‡Included changes to the statistical analyses and maintaining the randomisation sequence.
DMCs, data monitoring committee.

Interim analyses, stopping rules and early stopping

Few trials that reported a DMC reported on any interim analyses (n=14/55, 25%) (table 2). Only 22% (n=12/355) of the trials reported stopping rules. Thirteen trials (4%) reported early stopping; reasons included inadequate recruitment (n=5/13, 38%), futility (n=5/13, 38%), benefit of the treatment (n=2/13, 15%) and funding limitations (n=1/13, 8%). No trial reported early stopping due to harms. Less than one-third (n=4/13, 31%) of trials that reported early stopping also reported stopping rules.

Adverse events and harm-related endpoints

Less than half (n=134/300, 45%) of the trials reported a plan to collect data on adverse events in the methods section of the publication (table 4). About one-third (n=109/300, 36%) of trials specified the method by which they planned to collect adverse events data.

More than half (n=157/300, 52%) of the trials did not report any data related to adverse events. This included 11% (n=15/134) of the trials that reported a plan to collect and 12% (n=13/109) of the trials that specified a method for collecting adverse events data. Among the 48% (n=143/300) of trials that reported data on adverse events, 36% (n=52/143) reported severe harms, 11% (n=16/143) reported any harm (not individually described), 9% (n=13/143) reported organ system level harms and 74% (n=106/143) reported specific harms. Twenty-two trials (n=22/143, 15%) reported that no adverse events occurred. When adverse events data were reported, most trials (n=119/143, 83%) reported these by group (ie, intervention vs control, as opposed to aggregated data).

Seventy-two per cent (n=215/300) of trials reported information on harm-related endpoints. Among these, 25% (n=54/215) reported discontinuations due to adverse events and 22% reported deaths during the trial (n=47/215). Fifty-three per cent (n=114/215) of these trials reported withdrawals for which the reason was either unknown or not disclosed by the authors. About one-quarter (n=57/215, 27%) of these trials reported that there were no withdrawals or discontinuations due to adverse events.

Trials that reported the presence of a DMC were more likely to report data on adverse events (n=43/55, 78% vs n=100/245, 41%; p<0.001) and harm-related endpoints (n=52/55, 95% vs n=163/245, 67%; p<0.001) (table 5). Adverse events data were most commonly reported among trials that examined vaccines (n=12/14, 86%) and drugs (n=70/85, 82%) and infrequently reported among trials that examined communication, organisational or educational programmes (n=4/52, 8%) and rehabilitation or psychosocial interventions (n=4/30, 13%) (p<0.001). Harm-related endpoints data were most commonly reported among trials that examined vaccines (n=14/14, 100%), drugs (n=69/85, 81%), medical devices (n=20/29, 69%), surgery or radiotherapy (n=6/9, 67%) and rehabilitation or psychosocial interventions (n=20/30, 67%). They were less commonly reported among trials that examined prevention or screening programmes (n=8/14, 57%), communication, organisational or educational programmes (n=28/52, 54%)

Table 3 Reported presence of a data monitoring committee stratified by trial characteristics

Trial characteristic	N	Data monitoring committee, N (%)		P value
		Reported 55 (18)	Not reported 245 (82)	
Number of centres				
Single centre	139	14 (10)	125 (90)	<0.001
Multicentre	132	41 (31)	91 (69)	
Unclear	29	0 (0)	29 (100)	
Number of nations				
Single nation	281	48 (17)	233 (83)	0.06
Multinational	19	7 (37)	12 (63)	
Sample size				
N randomised, median (range)	300	224 (10–60480)	91 (10–9528)	<0.001
Nature of the intervention				
Drug	85	27 (32)	58 (68)	0.001
Vaccine	14	5 (36)	9 (64)	
Rehabilitation or psychosocial	30	1 (3)	29 (97)	
Prevention or screening	14	3 (21)	11 (79)	
Surgery or radiotherapy	9	0 (0)	9 (100)	
Communication, organisational or educational	52	4 (8)	48 (92)	
Alternative therapeutic	14	4 (29)	10 (71)	
Device	29	2 (7)	27 (93)	
Other*	53	9 (17)	44 (83)	
Primary outcome type				
Behavioural	46	4 (9)	42 (91)	0.16
Biomarker	55	12 (22)	43 (78)	
Pain	14	3 (21)	11 (79)	
Physiological	130	31 (24)	99 (76)	
Psychological	28	2 (7)	26 (93)	
Techniques/training	13	1 (8)	12 (92)	
Quality of life	5	0 (0)	5 (100)	
Other	9	2 (22)	7 (78)	
Industry or pharmaceutical funding				
Yes	50	16 (32)	34 (68)	0.009
No	250	39 (16)	211 (84)	

*Included therapeutic nutritional interventions (eg, supplements, infant formula and probiotics), sensorimotor interventions, physical activity interventions and financial interventions.

and alternative therapeutic interventions (n=8/14, 57%) (p=0.002).

DISCUSSION

Of the trials that we evaluated, 18% reported a DMC. This compares to 14% for paediatric trials published in 2005–2007[7] and 2% for those published in 1996–2002,[8] according to earlier reviews. As children are a vulnerable population, some would suggest that all paediatric trials should be overseen by a DMC.[10] Nevertheless, the decision whether to establish a DMC in a paediatric trial is dependent on various considerations (clinical, methodological and otherwise),[15] most of which are not available in published reports. It is thus likely that a number of the trials in our sample did not require a DMC; however, it is encouraging that their establishment was more frequent among those that investigated drugs, vaccines and alternative therapeutic interventions compared with those that investigated behavioural, rehabilitation or psychosocial programmes. Notably, the reporting of a DMC was

Table 4 Reporting of adverse events and harm-related endpoints

Trial characteristic	N total	N (%)
Plans to collect data on adverse events or side effects (in methods)		
Reported	300	134 (45)
Not reported		166 (55)
Method for collecting adverse events data		
Specified	300	109 (36)
Not specified		191 (64)
Adverse events*		
Reported data on harms	300	143 (48)
Reported severe harms		52/143 (36)
Reported any harm (not individually described)		16/143 (11)
Reported organ-system level harms		13/143 (9)
Reported specific harms		106/143 (74)
Reported that no harms occurred		22/143 (15)
Did not report data on harms		157 (52)
Harm-related endpoints†		
Reported data on harm-related endpoints	300	215 (72)
Reported discontinuations due to adverse events		54/215 (25)
Reported unexplained withdrawals		114/215 (53)
Reported mortality		47/215 (22)
Reported no discontinuations due to adverse events		57/215 (27)
Did not report data on harm-related endpoints		85 (28)

*52 of the 121 trials (43%) that reported harms reported more than one type of harm.
†51 of the 158 trials (32%) that reported the occurrence of harm-related endpoints reported more than one type of harm-related endpoint.

infrequent among trials that investigated surgeries, radiotherapy or devices where, especially in paediatric populations, their establishment may be warranted.

Less than half of the trials in our sample reported data on harms, a finding that compares to previous reviews of trials in specific topic areas. For example, Hum *et al*[10] noted suboptimal reporting of harms in paediatric trials of antibiotics for acute otitis media. Moreover, Leung *et al*[11] identified several methodological issues related to the identification and reporting of adverse events in paediatric studies of asthma medications. Incomplete reports of trials limit healthcare providers' ability to make decisions based on consideration of both the benefits and risks of available treatments.[24 25] We found that the reporting of adverse events was infrequent among trials that may be presumed to pose lesser risk (eg, communication, organisational or educational programmes and rehabilitation or psychosocial interventions); however, even in low-risk populations and putatively low-risk interventions, 'the balance of harms and benefits may easily lean toward harm'.[26]

Of the 143 trials that did report data on harms, 36% reported severe harms. Moreover, of the 215 trials that reported on harm-related endpoints, 54% reported discontinuations due to adverse events. By contrast, none of the trials in our sample reported early stopping due to harms. Ethically, trials must stop early when the findings of interim analyses show that exposing participants to additional potential risk by participating in the trial is not justified.[27] Thus, the occurrence of harms is not an indication to stop a trial, unless the accruing harms data show unreasonable risk from participation compared with the anticipated benefits.[27] An important issue is that more than half of the trials we analysed did not report any data related to harms. Because it is not possible to uphold ethical standards for trial conduct if harms data are not collected and monitored, this likely reflects a reporting issue. Similarly, a review of adverse event reporting in published and unpublished reports of studies of healthcare interventions found strong evidence that much of the information on adverse events remains unpublished.[28]

Implications for research and practice

Many trialists cite inadequate knowledge and paediatric-specific methodological training as serious barriers to the rigorous conduct and reporting of trials involving children.[29–31] Encouragement of prospective protocol publication, learning opportunities for trialists and trainees and the vigilant review of the reporting of DMCs and adverse events data by reviewers and editors of academic journals may contribute to improvements in conduct and reporting. As it was not feasible in this study to appraise the independency of members of the DMCs from trial sponsors or investigators (which is necessary to ensure unbiased monitoring), we cannot draw any conclusions regarding DMC conduct. Future studies may consider addressing this knowledge gap.

Strengths and limitations

We evaluated trials published in 2012, providing a baseline for ongoing evaluation of safety monitoring procedures in paediatric trials; however, the findings may not be reflective of present-day conduct and reporting. Moreover, because we investigated a random sample of trials, not all of the trials would have required a DMC. Nevertheless, ongoing evaluation of the state of the research is needed to evaluate changes over time and identify the areas in most need of attention. The random nature of our sample facilitated comparisons with previous studies,

Table 5 Reporting of adverse events and harm-related endpoints stratified by the nature of the intervention

Nature of the intervention	N	Reported data on adverse events, N (%)		P value	Reported data on harm-related endpoints, N (%)		P value
		Yes 143 (48)	No 157 (52)		Yes 215 (72)	No 85 (28)	
Data monitoring committee							
Reported	55	43 (78)	12 (22)	<0.001	52 (95)	3 (6)	<0.001
Not reported	245	100 (41)	145 (59)		163 (67)	82 (34)	
Nature of the intervention							
Drug	85	70 (82)	15 (18)	<0.001	69 (81)	16 (19)	0.002
Vaccine	14	12 (86)	2 (14)		14 (100)	0 (0)	
Rehabilitation or psychosocial	30	4 (13)	26 (87)		20 (67)	10 (33)	
Prevention or screening	14	5 (36)	9 (64)		8 (57)	6 (43)	
Surgery or radiotherapy	9	5 (56)	4 (44)		6 (67)	3 (33)	
Communication, organisational or educational	52	4 (8)	48 (92)		28 (54)	24 (46)	
Alternative therapeutic	14	9 (64)	5 (36)		8 (57)	6 (43)	
Device	29	16 (55)	13 (45)		20 (69)	9 (31)	
Other*	53	18 (34)	35 (66)		42 (79)	11 (21)	

*Included therapeutic nutritional interventions (eg, supplements, infant formula and probiotics), sensorimotor interventions, physical activity interventions and financial interventions.

including a similar descriptive analysis of paediatric trials published in 2007.[9]

Limitations of our findings stem from our reliance on the data provided in published reports. Because the reporting of serious adverse events is a regulatory requirement for many clinical trials, it is likely that our findings represent reporting shortcomings. Moreover, we examined only whether adverse events were reported, not whether the adverse events investigated were appropriate or adequate. Because we sampled trials published in 2012 covering various conditions, interventions and outcomes, our findings may not be generalisable to trials of specific conditions or interventions, measuring specific outcomes or published in other years.

CONCLUSIONS

The reporting of a DMC was infrequent within our sample. It was more common among trials that investigated drugs, vaccines and alternative therapies, multicentre trials, industry-sponsored trials and those that enrolled larger samples. Adverse events data were reported in less than half of the trials, which has important implications for the ability of paediatric trials to inform clinical decision making.[24 25] None of the trials in our sample reported early stopping due to harms.

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Contributors MPD conceptualised the study, designed the data collection instrument, oversaw all aspects of the work, verified and analysed the extracted data and contributed to drafting the manuscript. AG verified and analysed the extracted data, contributed to drafting the manuscript and revised the manuscript following input from the coauthors. PC, SC, LD, LH, LEK, RMF, KaW and KeW contributed to the interpretation of the extracted data and revised manuscript drafts critically for important intellectual content. BV contributed to the data analysis and interpretation of the extracted data and revised manuscript drafts critically for important intellectual content. All authors approved the manuscript as submitted and agree to be accountable for all aspects of the work.

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REFERENCES

1. DeMets DL, Ellenberg SS. Data monitoring committees - expect the unexpected. *N Engl J Med* 2016;375:1365–71.
2. US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, et al. *Guidance for clinical trial sponsors. Establishment and operation of clinical trial data monitoring committees*. Silver Spring, Maryland: Food and Drug Administration, 2006. https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm127073.pdf. (Accessed 28 Nov 2018).
3. *European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on data monitoring committees*. London, United Kingdom: European Medicines Agency, 2005. https://www.ema.europa.eu/documents/scientific-guideline/guideline-data-monitoring-committees_en.pdf. (Accessed 23 Nov 2018).
4. *National Institutes of Health. Data and safety monitoring board (DSMB) guidelines*. Betheseda, Maryland: National Institutes of Health, 2018. https://www.nidcr.nih.gov/research/human-subjects-research/interventional-studies/data-and-safety-monitoring-board-guidelines. (Accessed 23 Nov 2018).
5. Calis KA, Archdeacon P, Bain R, *et al*. Recommendations for data monitoring committees from the Clinical Trials Transformation Initiative. *Clin Trials* 2017;14:342–8.
6. Lin JY, Lu Y. Establishing a data monitoring committee for clinical trials. *Shanghai Arch Psychiatry* 2014;26:54–6.
7. Fernandes RM, van der Lee JH, Offringa M. A systematic review of the reporting of data monitoring committees' roles, interim analysis and early termination in pediatric clinical trials. *BMC Pediatr* 2009;9:77.
8. Sammons HM, Gray C, Hudson H, *et al*. Safety in paediatric clinical trials-a 7-year review. *Acta Paediatr* 2008;97:474–7.
9. Hamm MP, Hartling L, Milne A, *et al*. A descriptive analysis of a representative sample of pediatric randomized controlled trials published in 2007. *BMC Pediatr* 2010;10:96.
10. Hum SW, Golder S, Shaikh N. Inadequate harms reporting in randomized control trials of antibiotics for pediatric acute otitis media: a systematic review. *Drug Saf* 2018;41:933–8.
11. Leung JS, Johnson DW, Sperou AJ, *et al*. A systematic review of adverse drug events associated with administration of common asthma medications in children. *PLoS One* 2017;12:e0182738.
12. Hartling L, Wittmeier KD, Caldwell P, *et al*. StaR child health: developing evidence-based guidance for the design, conduct, and reporting of pediatric trials. *Pediatrics* 2012;129 Suppl 3(Suppl 3):S112–S117.
13. Caldwell PH, Dans L, de Vries MC, *et al*. Standard 1: consent and recruitment. *Pediatrics* 2012;129 Suppl 3(Suppl 3):S118–S123.
14. Hartling L, Hamm M, Klassen T, *et al*. Standard 2: containing risk of bias. *Pediatrics* 2012;129 Suppl 3(Suppl 3):S124–S131.
15. Ellenberg S, Fernandes RM, Saloojee H, *et al*. Standard 3: data monitoring committees. *Pediatrics* 2012;129 Suppl 3(Suppl 3):S132–S137.
16. van der Tweel I, Askie L, Vandermeer B, *et al*. Standard 4: determining adequate sample sizes. *Pediatrics* 2012;129 Suppl 3(Suppl 3):S138–S145.
17. Sinha IP, Altman DG, Beresford MW, *et al*. Standard 5: selection, measurement, and reporting of outcomes in clinical trials in children. *Pediatrics* 2012;129 Suppl 3(Suppl 3):S146–S152.
18. Williams K, Thomson D, Seto I, *et al*. Standard 6: age groups for pediatric trials. *Pediatrics* 2012;129 Suppl 3(Suppl 3):S153–S160.
19. Gates A, Hartling L, Vandermeer B, *et al*. The conduct and reporting of child health research: An analysis of randomized controlled trials published in 2012 and evaluation of change over 5 years. *J Pediatr* 2018;193:237–44.
20. Gates A, Caldwell P, Curtis S, *et al*. Consent and recruitment: the reporting of paediatric trials published in 2012. *BMJ Paediatr Open* 2018;2:e000369.
21. Cochrane. *Cochrane Central Register of Controlled Trials (CENTRAL)*. London, United Kingdom: Cochrane. c, 1999-2018. http://www.cochranelibrary.com/about/central-landing-page.html. (Accessed 8 Feb 2019).
22. Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)-a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
23. World Health Organization. International statistical classification of diseases and related health problems 10th revision. 2016 http://apps.who.int/classifications/icd10/browse/2016/en (Accessed 23 Nov 2018).
24. Lineberry N, Berlin JA, Mansi B, *et al*. Recommendations to improve adverse event reporting in clinical trial publications: a joint pharmaceutical industry/journal editor perspective. *BMJ* 2016;355:i5078.
25. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomized trials. *J Clin Epidemiol* 2010;2010:834–40.
26. Ioannidis JP, Greenland S, Hlatky MA, *et al*. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet* 2014;383:166–75.
27. Deichmann RE, Krousel-Wood M, Breault J. Bioethics in practice: Considerations for stopping a clinical trial early. *Ochsner J* 2016;16:197–8.
28. Golder S, Loke YK, Wright K, *et al*. Reporting of adverse events in published and unpublished studies of health care interventions: A systematic review. *PLoS Med* 2016;13:e1002127.
29. Duffett M, Choong K, Foster J, *et al*. High-quality randomized controlled trials in pediatric critical care: A survey of barriers and facilitators. *Pediatr Crit Care Med* 2017;18:405–13.
30. Hamm MP, Scott SD, Klassen TP, *et al*. Do health care institutions value research? A mixed methods study of barriers and facilitators to methodological rigor in pediatric randomized trials. *BMC Med Res Methodol* 2012;12:158.
31. Joseph PD, Craig JC, Tong A, *et al*. Researchers', regulators', and sponsors' views on pediatric clinical trials: A multinational study. *Pediatrics* 2016;138:e20161171.