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Consent and recruitment in pediatric research: an evaluation of trials published in 2012

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ABSTRACT

Objectives. We evaluated 300 pediatric trials to determine: the consent and recruitment strategies used; how trial information was presented to families; how incentives were used; and if they achieved their recruitment targets.

Methods. For this cross-sectional evaluation, we searched the Cochrane Central Register of Controlled trials for pediatric trials published in 2012 and randomly selected 300 that reported on outcomes for participants aged ≤21 years. We collected data on consent and recruitment procedures for each trial and undertook descriptive analyses in SPSS Statistics.

Results. All but one trial (99.7%) used a standard recruitment strategy. Most (92%) trials reported that consent was obtained but only 13% reported who obtained consent. Two-thirds (65%) of trials included school-aged participants, and of these 68% reported obtaining assent. Half (50%) of the trials reported who the trial information was targeted to. Most trials (75%) of school-aged participants targeted information toward children or children and their parents. Fourteen percent of trials reported using incentives, half (50%) of which were in the form of compensation. Only 48% of trials reported sufficient data to determine if their recruitment targets were achieved. Of these, 70% achieved their targets.

Conclusions. Notable reporting shortcomings included: how families were recruited into the trial; who obtained consent and/or assent and how; who trial information was directed to; whether incentives were used; and sufficient data to determine if the recruitment target was achieved. Forthcoming pediatric-specific reporting standards may improve reporting in this priority area. Our data provide a baseline for ongoing monitoring of the state of the research.

WHAT IS KNOWN ABOUT THE SUBJECT

- In 2012, Standards for Research in (StaR) Child Health published evidence-based guidance to inform ethically-sound recruitment and consent in pediatric trials, and identified knowledge gaps.
- To optimize the value of children's participation in research, trialists must safeguard them from avoidable harm, use rigorous methodologies, and report their findings transparently.

WHAT THIS STUDY ADDS

- We collected data on the reporting of consent and recruitment procedures from a random sample of 300 pediatric trials published in 2012.
- Reporting shortcomings included: how families were recruited; who obtained consent/assent; who trial information was directed to; whether incentives were used; if recruitment targets were reached.
- The data from this study will serve as a baseline for ongoing monitoring and evaluation of the state of the research.

INTRODUCTION

In 2012, Standards for Research in (StaR) Child Health published six evidence-based Standards to guide the rigorous design, conduct, and reporting of pediatric trials.[1, 2] Each Standard[3-8] includes practice recommendations and a research agenda to address knowledge gaps. To characterize the state of the literature, we analyzed a random sample of 300 pediatric trials published in 2012[9] and identified various shortcomings in their conduct and reporting. Among other issues, most trials reported results that were at unclear or high risk of bias, and only 46% were registered in a clinical trial registry.[9]

Trialists are ethically obligated to optimize the value of children's participation in research by safeguarding them from avoidable harms,[10, 11] using rigorous methodologies,[12] and reporting their findings transparently.[13] Ethically-sound recruitment and consent procedures include: obtaining consent from parents and assent from children; approaching all eligible children, and providing families with age-appropriate trial information; ensuring that incentives do not influence children's decision-making; and clearly differentiating between elements of standard care and those that are part of the trial.[3] Safeguarding children from avoidable harm also includes carefully planned recruitment targets. Trials that recruit too many participants needlessly expose children to the burdens of research participation, while those that are underpowered to detect clinically meaningful effects contribute to research waste.[14]

In response to the knowledge gaps and priorities identified by the Consent and Recruitment Standard Development Group, we evaluated the consent and recruitment procedures for 300 pediatric trials to determine: the consent and recruitment strategies used; the formats used to present trial information to families; how incentives were used; and whether they achieved their recruitment targets.

METHODS

Context

The analyses presented herein are part of a larger study[9, 15] in which we characterized the conduct and reporting qualities of 300 pediatric trials published in 2012. A full description of the study methods appears in a previous publication.[9]

Database search

In November 2013, we searched the Cochrane Central Register of Controlled Trials for randomized trials published in 2012 (Supplementary File 1). The Cochrane Central Register of Controlled Trials is a comprehensive database of reports of randomized and quasi-randomized trials, taken mainly from MEDLINE and Embase.[16] The 2012 publication date coincided with the publication of the StaR Child Health Standards.

Trial selection

We identified 2296 unique records via the search. We ordered these randomly in Excel (v. 2016; Microsoft Corporation, Redmond, Washington) and selected the first 300 published trials that reported on outcomes specific to participants ≤21 years of age (mean age at baseline). The sample size coincides with our previous evaluations of pediatric trials published in 2007.[15] We did not restrict our sample by language, condition, intervention, or outcome type.

Data extraction

For each included trial, we extracted data into REDCap (Research Electronic Data Capture)[17] pertaining to the characteristics of the: publication; trial design; intervention; trial conduct; trial sample; data monitoring committee and follow-up; outcomes and conclusions; risk of bias; and trial registration and protocol.[9] We also collected additional data to address the knowledge gaps and priorities outlined by the Standard Development Groups. An author (AG or MPD) verified the extracted data to identify errors or omissions.

Our data extraction guide for the variables included in this report is in Supplementary File 2. We classified the primary diagnostic category according to the World Health Organization's International Statistical Classification of Diseases and Related Health Problems 10th Revision.[18] We classified participants' recruitment location according to the International Monetary Fund classification system.[19] We classified the recruitment strategy as standard if the participants provided consent and were then randomized in a typical manner (e.g., 1:1, 1:2). We classified the reasons for recruitment delays based on the definitions provided by Kaur et al.[20] We categorized incentives as one or more of the following: reimbursements (costs associated with participation that are paid back, e.g., parking, travel); compensation (participants are paid a modest amount for their time and effort); tokens of appreciation (a small gift given at the end of the trial, usually not known beforehand); and incentive payments (typically known before participation and used to enhance recruitment).

We referred to protocols, trial registries, and associated publications to complement data extraction. We searched for trial registers in the International Clinical Trials Registry Platform, the ISRCTN Registry, and via Google. We located trial registers for 46% (n = 138/300) of the trials.[9] We used protocols or companion articles only when cited in the publications. We did not contact authors to collect consent and recruitment details beyond those in published reports.

Data analysis

We exported the data to an Excel workbook for cleaning and to SPSS Statistics (v. 23; IBM Corporation, Armonk, New York) for descriptive analysis. We determined whether the recruitment target was reached by comparing the result of the sample size calculation to the number of participants enrolled in the trial.

RESULTS

Patient population and consent and recruitment procedures

Table 1 shows details of the patient population and consent and recruitment procedures. Most trials recruited from established market economies[19] (n = 188/300, 63%) and 68% (n = 205/300) reported excluding patients with co-morbid or chronic diseases. Only one trial (n = 1/300, 0.3%) reported using a non-standard recruitment strategy (Zelen's design). Only one trial (n = 1/300, 0.3%) reported a specified amount of time (seven days) for participants to decide whether to enroll. Seventeen percent (n = 51/300) of trials reported who first spoke to the family about participating. The most common point of contact was a researcher or clinician unknown to the participant (n = 28/51, 55%).

Most trials reported that consent was obtained (n = 275/300, 92%), but only 13% (n = 39/300) reported who obtained consent. Ninety percent (n = 270/300) of trials reported how consent was provided. Among these, 55% (n = 149/270) obtained consent via parental permission and 43% (n = 117/270) via parental permission combined with participant assent. Four trials (2%) reported only obtaining the consent of a mature minor. These included trials of the following: corrective exercises for scoliosis; prevention of acute knee injuries in athletes; bright-light therapy of non-seasonal depression; and oxidant and antioxidant levels in patients with orthodontic tooth movement. Of trials that included school-aged participants (>5 years old; n = 196/300, 65%), 68% (n =117/172) reported obtaining participant assent and 32% (n = 55/172) reported obtaining parental permission only. Three percent (n =

9/300) of trials reported that participants and families were involved in the design or conduct of the trial.

Nineteen percent (n = 56/300) of trials did not report the recruitment setting (or it was unclear). When clearly reported, most often trials recruited participants from inpatient populations (n = 74/300, 25%), outpatient populations (n = 51/300, 17%), or schools (n = 70/300, 23%).

Table 1. Characteristics of the patient populations and recruitment approaches (N = 300)

Characteristic	**n (%)**
Recruitment location*	
Established market economy	188 (62.7)
Transitional country	19 (6.3)
Developing country	96 (32.0)
Primary diagnostic category**	
Mental and behavioral disorders	50 (16.7)
Infectious and parasitic disease	39 (13.0)
Respiratory system	30 (10.0)
Conditions originating in the perinatal period	28 (9.3)
Endocrine, nutritional, and metabolic diseases	25 (8.3)
Oral health	19 (6.3)
Factors influencing health status and contact with health services	13 (4.3)
Digestive system	10 (3.3)
Blood, blood forming organs, and immune mechanism	7 (2.3)
Congenital malformations, deformations, and chromosomal abnormalities	7 (2.3)
Nervous system	7 (2.3)
Eye and adnexa	5 (1.7)
Ear and mastoid process	4 (1.3)
Injury, poisoning, and consequences of external causes	4 (1.3)
Circulatory system	3 (1.0)
External causes of morbidity and mortality	3 (1.0)
Genitourinary system	3 (1.0)
Musculoskeletal system and connective tissue	3 (1.0)
Neoplasms	3 (1.0)
Pregnancy, childbirth, and the puerperium	2 (0.7)
Skin and subcutaneous tissue	2 (0.7)
Other	33 (11.0)
Exclusion of patients with chronic diseases	
Yes	205 (68.3)
No	59 (19.7)
Unclear	36 (12.0)
Recruitment strategy	

Standard	299 (99.7)
Not standard	1 (0.3)
Time to decide whether to enroll	
Limited	1 (0.3)
Not reported	299 (99.7)
Who first approached the patient	
Child's clinician	8 (2.7)
Researcher or clinician unknown to patient	28 (9.3)
Other	15 (5.0)
Not reported	249 (83.0)
Consent obtained and reported	
Yes	275 (91.7)
No	25 (8.3)
Who obtained consent	
Child's clinician	2 (0.7)
Researcher or clinician unknown to patient	31 (10.3)
Other	6 (2.0)
Not reported	261 (87.0)
How consent was provided	
Parental permission	149 (49.7)
Parental permission and participant assent	117 (39.0)
Consent of a mature minor	4 (1.3)
Not reported	30 (10.0)
Patients/families involved in trial design/conduct	
Reported	9 (3.0)
Not reported	291 (97.0)
Source of recruitment* **	
Inpatients	74 (24.7)
Outpatients	51 (17.0)
Clinician's office	38 (12.7)
School	70 (23.3)
Community	44 (14.7)
Other	14 (4.7)
Unclear or not reported	56 (18.7)

*Defined according to the International Monetary Fund classification system (2013).[19] Totals to 303 because three trials recruited from more than one category.

**Defined according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (2010).[18] These data have been previously reported, but are shown here for context.[9]

***Total exceeds 300 because some trials reported multiple sources.

Formats used to present trial information to participants and families

About two-thirds (n = 184/300, 61%) of trials reported how families were informed about the opportunity to participate (Table 2). Of these, 59% (n = 108/184) reported that parents were

approached during a healthcare visit, 8% (n = 15/184) used mail invites, 4% (n = 7/184) approached parents by telephone, 14% (n = 26/184) used media messages (e.g., via the radio, newspaper, or a website), and 11% (n = 20/184) used pamphlets. Other methods (n = 63/184, 34%) included schools (i.e., school staff contacted parents about the trial), community contacts and word of mouth; and identifying potential participants through chart reviews or previous trials. Sixteen percent (n = 30/184) of trials used multiple means of informing families about the opportunity to participate.

Half (n = 151/300, 50%) of the trials reported the person who was the target of the trial information. Of these, 58% (n = 88/151) targeted the information toward parents, 37% (n = 56/151) toward parents and children, and 5% (n = 7/151) toward children only. Although it was not reported, we assumed that an additional 13% (n = 40/300) intended the information to be for parents, as participants were infants or children less than school age. When it was reported, all trials that included only participants ≤5 years of age directed the information to parents only (n = 64/64, 100%). Most trials (n = 65/87, 75%) that included participants >5 years of age directed trial information either to children or both parents and children. All of the trials (n = 5/5, 100%) in which information was directed specifically toward children were conducted in adolescents.

Table 2. Formats used to present trial information to participants and families (N = 300)

Characteristic	**n (%)**
How the family heard about the trial*	
Approached during healthcare visit	108 (36.0)
Mailing	15 (5.0)
Generalized mailing	4 (1.3)
Targeted mailing	9 (3.0)
Personalized mailing	2 (0.7)
Phone calls	7 (2.3)
Media	26 (8.7)
Pamphlets	20 (6.7)
Other	63 (21.0)
Not reported	116 (38.7)
Who trial information was targeted to	
Parents	88 (29.3)
Children	7 (2.3)
Parents and children	56 (18.7)
Not reported	149 (49.7)

*Total exceeds 300 because some trials used multiple approaches.

Use of incentives

Most trials did not report whether incentives were used (n = 253/300, 84%) and five (2%) reported not using incentives (Table 3). Fourteen percent (n = 42/300) of trials reported using incentives. These were most often in the form of compensation (n = 21/42, 50%) or tokens of appreciation (n = 12/42, 29%). Reported compensation amounts varied, e.g., free dental care and $20 for families participating in a 5-year dental amalgam trial; $5 to $10 gift cards for adolescents participating in a trial of telephone-based preventive health education and counseling. Tokens of appreciation also varied, e.g., an insecticide impregnated bed net and soap for families participating in a trial of therapeutic food for catch-up growth after malaria; $40 for teachers participating in a trial of a school-based intervention.

The child was often the recipient of the incentive, rather than the parents or family: 20% (n =1/5) of reimbursements (e.g., $5 for a bus ticket for travel for adolescents participating in a trial of exercise training for obesity), 48% (n = 10/21) of compensation incentives (e.g., $10 for completing a survey for adolescents participating in a trial of a preventive family intervention), 50% (n = 6/12) of tokens of appreciation (e.g., $10 gift certificate for completing a five week trial of coping skills training for adolescents with asthma, and a six week follow-up assessment), and 83% (n = 5/6) of incentive payments (e.g., $50 supermarket gift cards for adolescents participating in a trial of a multicomponent dietary intervention) were intended for the participant.

Table 3. Use of incentives (N = 300)

Characteristic	**n (%)**
Use of incentives	
Yes	42 (14.0)
No	5 (1.7)
Not reported	253 (84.3)
Type(s) of incentives used*	
Reimbursements	5/42 (11.9)
Compensation	21/42 (50.0)
Tokens of appreciation	12/42 (28.6)
Incentive payments	6/42 (14.3)

*Total exceeds 42 because some trials used multiple types of incentives.

Recruitment target attainment

About half (n = 145/300, 48%) of the trials reported sufficient information to determine if the recruitment target was achieved (Table 4). Of these, 70% (n = 102/145) recruited their target sample size. Recruitment delays were reported in 6% (n = 19/300) of trials, and were most often due to patient level (n = 10/19, 53%; e.g., travel, duration of trial, preferences) or trial level factors (n = 9/19, 47%; e.g.,

funding, trial management, feasibility). Strategies to address recruitment delays included stopping the trial before the recruitment target was achieved (n = 13/19, 68%), extending the recruitment period (n = 3/19, 16%), adding trial sites (n = 2/19, 11%), modifying the eligibility criteria (n = 3/19, 16%), and modifying the incentives (n = 1/19, 5%).

Table 4. Recruitment target attainment (N = 300)

Characteristic	**n (%)**
Sample size	
Calculation reported	155 (51.7)
Recruitment target reached*	102/145 (70.3)
Recruitment delays reported	
Yes	19 (6.3)
No	281 (93.7)
Types of recruitment delays**	
Trial level factors	9/19 (47.4)
Site level factors	1/19 (5.3)
Patient level factors	10/19 (52.6)
Trial team level factors	1/19 (5.3)
Not specified	4/19 (21.1)
How recruitment delays were addressed***	
Extending the recruitment period	3/19 (15.8)
Adding additional trial sites	2/19 (10.5)
Modifying the eligibility criteria	3/19 (15.8)
Modifying incentives	1/19 (5.3)
Stopping the trial before reaching the target	13/19 (68.4)

*Based on sample size calculation and number randomized; data for this calculation were unavailable for 10 trials that reported a sample size calculation.
**Total exceeds 19 because some trials reported more than one type of delay.
***Total exceeds 19 because some trials reported more than one method.

DISCUSSION

This study addresses some of the knowledge gaps and priorities identified by StaR Child Health's Consent and Recruitment Standard Development Group.[3] We found that details of consent and recruitment procedures were infrequently reported within publications of pediatric trials. Although most trials reported obtaining consent, elaboration on the consent and recruitment process was not common.

Despite being widely accepted as a requirement,[11, 21] there remains ambiguity about what constitutes assent in pediatric trials,[22] which children are capable of providing it,[22] and how it should be reported.[23] Recently, Tait and Geisser (2017) established an operational definition of assent, including

recommendations about the level of information appropriate for different ages.[24] Nevertheless, guidance on the age at which children must provide assent varies substantially by country.[25-27] It also remains unclear whether the level of detail regarding consent and recruitment procedures required by research ethics boards is appropriate or necessary in published reports of pediatric trials. In 2010, Saint-Raymond et al. called attention to the need for reporting guidelines specific to research with children.[23] The development of pediatric adaptations of the Standard Protocol Items: Recommendations for Interventional Trials[28] and Consolidated Standards of Reporting Trials[29] statements is underway.[30]

Fewer than 20% of trials reported who approached families to participate. Although a relationship to the person obtaining consent can encourage recruitment,[31] when the person is the child's healthcare provider parents may worry that refusing participation will impact their child's quality of care.[22] In most trials of school-aged children, trial information was directed to both parents and children. Parents' and children's understanding of trial materials are fundamental to ethical and efficient recruitment.[3] Not understanding trial information discourages parents and children from enrolling in trials,[31] and typical presentations of the benefits and risks of trial participation are often difficult for parents to understand.[32] The integrated consent model in which clinicians engage the trial participant in a consent conversation similar to usual care and additionally present the opportunity for the randomization of previously validated treatment options, has been proposed.[33] This approach has been suggested for low-risk and pragmatic trials,[33] however the applicability to pediatric trials needs to be established.

Few trials reported whether incentives were used, but of those that did, many were intended for children. Trial participation can be costly for families, and there is general consensus that they should be reimbursed for the related expenses (e.g., travel, parking) at a rate that is sufficient but does not lead them to undervalue risks or coerce them to consent.[22, 31] As children value incentives differently than adults, their provision to minors is controversial.[3, 10] When incentives are used, it is critical that children understand the implications of the trial and that the incentives do not influence their decision to participate.[3, 10]

Seventy percent of trials met their recruitment targets. This is substantially greater than the 29% reported in St-Louis et al.'s review of pediatric general surgical trials,[34] and the 55% in Sully et al.'s review of multicenter trials in the United Kingdom.[35] Failing to meet the recruitment target contributes to research waste when the trial is underpowered to detect clinically important differences.[36] Due to

reporting deficiencies, we could only ascertain whether trials achieved their recruitment targets for half of the sample. Whether transparent reporting is biased toward trials that meet their recruitment targets is not yet known.

Strengths and Limitations

We have highlighted a number of conduct and/or reporting gaps in an effort to contribute to the ongoing research agenda. Our sample will serve as a baseline for ongoing monitoring of consent and recruitment procedures in pediatric trials. The extracted data were limited to those available within published reports, therefore we cannot ascertain the extent to which the findings reflect conduct and/or reporting shortcomings. We used a sample of trials published in 2012, and the findings may not be generalizable to other years.

CONCLUSIONS

In our sample, five reporting shortcomings were evident: how families were recruited; who obtained consent and/or assent and how; who trial information was directed to; whether incentives were used; and sufficient data to determine if the recruitment target was met. Forthcoming reporting guidance specific to pediatric trials[30] and the StaR Child Health Standards[3] may contribute to improving the conduct and reporting of pediatric trials in this priority area. Using this study as a baseline, continued monitoring of the state of the research will allow for the identification of changes over time and the need for knowledge translation efforts.

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COMPETING INTERESTS

We have no financial or other conflicts of interest to declare.

CONTRIBUTORS' STATEMENT

Dr Dyson conceptualized the study, designed the data collection instrument, supervised all aspects of the work, verified and analyzed the extracted data, and contributed to drafting the manuscript.
Dr Gates verified and analyzed the extracted data, contributed to drafting the manuscript, and completed revisions of the manuscript drafts following input from the other authors.
Drs Caldwell, Curtis, Dans, Hartling, Kelly, Fernandes, Woolfall, and Williams contributed to the interpretation of the extracted data, and revised manuscript drafts critically for important intellectual content.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DATA SHARING STATEMENT

The data collected and analyzed from trials included in this study will be available to researchers via reasonable request from the corresponding author. The data will be available immediately following, and for 5 years after article publication. Our data extraction guide is available as a supplementary file.

PREVIOUS PRESENTATION

Parts of this research were presented as a poster at our local research day (Pediatric Research Day, Department of Pediatrics, University of Alberta, Edmonton, Canada) on 16 May 2018 under the following title: "The safe and ethical participation of children in research: a descriptive analysis of the conduct and reporting of trials published in 2012".

REFERENCES

1. Wittmeier KD, Craig J, Klassen TP, et al. The mission of StaR Child Health is to improve the quality of the design, conduct, and reporting of pediatric clinical research by promoting the use of modern research standards. Introduction. *Pediatrics* 2012;129(Suppl 3):S111.
2. 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):S112-17.
3. Caldwell PH, Dans L, de Vries MC, et al. Standard 1: consent and recruitment. *Pediatrics* 2012;129(Suppl 3):S118-23.
4. Ellenberg S, Fernandes RM, Saloojee H, et al. Standard 3: data monitoring committees. *Pediatrics* 2012;129(Suppl 3):S132-7.
5. Hartling L, Hamm M, Klassen T, et al. Standard 2: containing risk of bias. *Pediatrics* 2012;129(Suppl 3):S124-31.
6. 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):S146-52.
7. van der Tweel I, Askie L, Vandermeer B, et al. Standard 4: determining adequate sample sizes. *Pediatrics* 2012;129(Suppl 3):S138-45.
8. Williams K, Thomson D, Seto I, et al. Standard 6: age groups for pediatric trials. *Pediatrics* 2012;129(Suppl 3):S153-60.
9. 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.
10. Joseph PD, Craig JC, Caldwell PH. Clinical trials in children. *Br J Clin Pharmacol* 2015;79(3):357-69.
11. Graham A, Powell M, Taylor N, et al. Ethical research involving children: putting the evidence into practice. *Family Matters* 2015;96:23-8.
12. Ioannidis JP, Greenland S, Hlatky MA, et al. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet* 2014;383:166-75.
13. Glasziou P, Altman DG, Bossuyt P, et al. Reducing waste from incomplete or unusable reports of biomedical research. *Lancet* 2014;383:267-76.
14. Nayak BK. Understanding the relevance of sample size calculation. *Indian J Ophthalmol* 2010;58:469.

15. 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.
16. Cochrane. Cochrane Central Register of Controlled Trials (CENTRAL). London, United Kingdom: Cochrane. c1999-2018. Available from: http://www.cochranelibrary.com/about/central-landing-page.html. Accessed 5 September 2018.
17. 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.
18. World Health Organization. Classifications. International Classification of Diseases (ICD). ICD-10 online versions. Geneva, Switzerland: World Health Organization. 2018. Available from: http://www.who.int/classifications/icd/icdonlineversions/en/. Accessed 5 September 2018.
19. International Monetary Fund. World Economic and Financial Surveys. World Economic Outlook. Database-WEO Groups and Aggregates Information. Washington, District of Columbia: International Monetary Fund. 2013. Available from: http://www.imf.org/external/pubs/ft/weo/2013/02/weodata/groups.htm. Accessed 5 September 2018.
20. Kaur G, Smyth RL, Williamson P. Developing a survey of barriers and facilitators to recruitment in randomized controlled trials. *Trials* 2012;13:218.
21. General Assembly of the World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191-4.
22. Leibson T, Koren G. Informed consent in pediatric research. *Paediatr Drugs* 2015;17:5-11.
23. Saint-Raymond A, Hill S, Martines J, et al. CONSORT 2010. *Lancet* 2010;376(9737):229-30.
24. Tait AR, Geisser ME. Development of a consensus operational definition of child assent for research. *BMC Med Ethics* 2017;18:41.
25. Shaddy RE, Denne SC, The Committee on Drugs and Committee on Pediatric Research. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Pediatrics* 2010;125:850-60. Reaffirmed January 2014; 133:e1479.
26. Lepola P, Needham A, Mendum J, et al. Informed consent for paediatric clinical trials in Europe. *Arch Dis Child*. 2016;101:1017-25.
27. Canadian Paediatric Society. Ethical issues in health research in children. *Paediatr Child Health* 2008;13:707-20.

28. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200-7.
29. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Trials* 2010;11:32.
30. Clyburne-Sherin AVP, Thurairajah P, Kapadia MZ, et al. Recommendations and evidence for reporting items in pediatric clinical trial protocols and reports: two systematic reviews. *Trials* 2015;16:417.
31. Tromp K, Zwaan CM, van de Vathorst S. Motivations of children and their parents to participate in drug research: a systematic review. *Eur J Pediatr* 2016;175:599-12.
32. Tait AR, Voepel-Lewis T, Zikmund-Fisher BJ, et al. Presenting research risks and benefits to parents: does format matter? *Anesth Analg* 2010;111:718-23.
33. Kim SY, Miller FG. Informed consent for pragmatic trials: the integrated consent model. *NEJM* 2014;370:769-72.
34. St-Louis E, Oosenbrug M, Landry T, et al. Enrollment and reporting practices in pediatric general surgical randomized clinical trials: a systematic review and observational analysis. *J Pediatr Surg* 2018;53:879-84.
35. Sully BG, Julious SA, Nicholl J. A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies. *Trials* 2013;14:166.
36. Salman RA-S, Beller E, Kagan J, Hemminki E, et al. Increasing value and reducing waste in biomedical research regulation and management. *Lancet* 2014;383:176-85.

Supplementary File 1. Search Strategy

Summary of Search

Database	Date Searched	Number Retrieved	After Duplicate Removal
Cochrane Central Register of Controlled Trials (Wiley)	November 4, 2013	2343	2296
Total		**2343**	**2296**

Database: Cochrane Central Register of Controlled Trials (Wiley)

Date Searched: 4 November 2013 at 21:07:57.057

Results: 2343 records (2296 following duplicate removal)

Search Strategy:

#1 (Infant* or infancy or Newborn* or Baby* or Babies or Neonat* or Preterm* or Prematur* or Postmatur* or Child* or Schoolchild* or School age* or Preschool* or Kid or kids or Toddler* or Teen* or Boy* or Girl* or Minors* or Pubert* or Pubescen* or Prepubescen* or Pediatric* or Paediatric* or Peadiatric* or Nursery school* or Kindergar* or Primary school* or Secondary school* or Elementary school* or High school* or Highschool*):ti,ab,kw

#2 (Adolesc*):ti,ab

#3 (Infant or Child or Minors or Puberty or Pediatrics or Schools):kw

#4 #1 or #2 or #3

#5 adolescent*:kw

#6 (adolescent* and (adult* or elderly or "middle aged" or "aged, 80 and over")):kw

#7 #6 and not #4

#8 #4 or #5

#9 #8 and not #7 from 2012 to 2012, in Trials

Supplementary File 2. Data Extraction Guide

Field	Response	Comments
Trial conduct		
Where were participants recruited from?	□Established market economy □Transitional country □Developing country	Select all that apply. **Established market economy:** United States, Canada, Australia, New Zealand, Israel, Japan, Western European countries **Transitional country:** Eastern European countries: Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Hungary, Kosovo, Latvia, Lithuania, FYR Macedonia, Montenegro, Poland, Romania, Serbia, Turkey **Developing country:** All others *(Panagiotou BMJ 2013; International Monetary Fund http://www.imf.org/external/pubs/ft/weo/2013/02/weodata/groups.htm)*
What recruitment strategies were used?	□Standard □Not standard	**Standard:** Participants provide consent and then are randomized in a typical 1:1, 1:2, etc. manner. **Not standard:** Any of: – Open trial design (randomization occurs before participants are approached, so that participants are informed of the treatment they were randomized to receive prior to consent) – Increasing or decreasing the chance of receiving the experimental treatment – Experimental treatment for all participants and standard treatment for non-participants – Standard care for all participants and experimental treatment for non-participants – Random assignment of treatment for participants and choice of treatment for non-participants – Opt in or opt out recruitment (consent was sought for participation or non-participation)
Who first approached the patient about participating in the trial?	□Child's clinician □Researcher/clinician unknown to patient □Other (specify): □Not reported	Other professionals could include individuals such as teachers.
How did the family first hear about the trial?	□Approached during healthcare visit	Select all that apply.

Supplementary File 2. Data Extraction Guide

	□Generalized mailing □Targeted mailing □Personalized mailing □Phone calls □Media □Pamphlets □Not reported □Other (specify):	**Generalized mailing:** mail out to a large population **Targeted mailing:** mail out to a targeted group **Personalized mailing:** mailing addressed to the individual **Media:** Internet, newspaper, radio, TV **Pamphlets:** given to the families or left out for participants to pick up
Who was the trial information targeted to?	□Parents □Children □Both □Not reported	"Trial information" refers to recruitment materials.
Did the authors report that consent was obtained?	□Yes □No	
If yes, who obtained consent from the participants?	□Child's clinician □Researcher/clinician unknown to patient □Other (specify): □Not reported	Other professionals could include individuals such as teachers.
If yes, how was consent provided in the study?	□Parental permission □Parental permission and participant assent □Consent of a mature minor □N/A	Can assume parental consent if consent reported but not specified, and no other indication that another model was used.
Were any incentives used in the study?	□Yes □No □Not reported	
If yes, what incentives were used?	□Reimbursement □Parents □Child □Families (no other detail) □Not reported □Compensation □Parents □Child	Select all that apply. **Reimbursement:** costs associated with participation in the study (e.g., travel, parking) are paid back. **Compensation:** participants are paid a modest amount for their time/effort. **Appreciation:** a small token gift given at the end of the study, usually not known beforehand. **Payment:** typically known before study participation and used as a strategy

Supplementary File 2. Data Extraction Guide

	□Families (no other detail) □Not reported □Appreciation □Parents □Child □Families (no other detail) □Not reported □Payment □Parents □Child □Families (no other detail) □Not reported □N/A	to enhance recruitment. *Use "families" only if specified as such in the publication, with no information provided on whether the incentives were meant for the parents or child.
How long were participants given to decide whether or not to enroll in the trial?	□No restriction □Limited □No time □Not reported	**No restriction:** hours to weeks **Limited:** immediately to less than a few hours **No time:** retrospective consent
Were any delays, shortfalls, or difficulties in recruitment reported once the trial was underway?	□Yes □No	
If yes, what were the reasons for the delays or difficulties?	□Trial level factors □Site level factors □Patient level factors □Clinical team level factors □Information and consent factors □Study team level factors □Other (specify): □N/A	Examples (for more detail, see *Kaur Trials 2012*): **Trial level:** funding, trial management, feasibility **Site level:** competing projects, time to open up site **Patient level:** travel, costs, duration of trial and follow-up, preferences, language or cultural barrier **Information and consent:** amount and complexity of trial information provided, experience of clinical team seeking consent **Study team level:** experience and training of team, clinical workload, clinician attitude towards research or treatment
How were the recruitment delays or difficulties addressed?	□Described (specify): □Not described □No difficulties	
Was the use of patient or family involvement in the	□Yes (specify): □No	For involvement in the **conduct** of the study, consider involvement past the point where a decision is made to participate, i.e., the participant/family has

Supplementary File 2. Data Extraction Guide

design or conduct of the study reported?		already enrolled prior to the involvement referred to.
How was the study population selected?	□Inpatients □NICU □PICU □Not reported □Other (specify): □Outpatients □Clinicians' office □School □Community □Unclear □Other (specify):	Select all that apply. In the case of selection from a dental clinic, report "Doctor's office."
What primary diagnostic category was involved in the study?	□Infectious and parasitic diseases □Neoplasms □Blood, blood forming organs, and immune mechanism □Endocrine, nutritional, and metabolic diseases □Mental and behavioural disorders □Nervous system □Eye and adnexa □Ear and mastoid process □Circulatory system □Respiratory system □Digestive system □Skin and subcutaneous tissue □Musculoskeletal system and connective tissue □Genitourinary system □Pregnancy, childbirth, and the puerperium □Conditions originating in the perinatal period	Select the primary diagnostic category of the study using the ICD-10 classification system. *(ICD-10 Version:2010 http://apps.who.int/classifications/icd10/browse/2010/en)*

Supplementary File 2. Data Extraction Guide

	□Congenital malformations, deformations, and chromosomal abnormalities □Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified □Injury, poisoning, and consequences of external causes □External causes of morbidity and mortality □Factors influencing health status and contact with health services □Oral health □Other (specify):	
Did the study exclude participants who had at least one chronic condition (other than the condition that was the focus of the trial) or a co-morbid condition?	□Yes □No □Unclear	
Sample size		
How many patients were approached to participate in the study?		Use NR if applicable.
How many patients consented to participate in the study?		Use NR if applicable. *This is not necessarily the same number as randomized.
How many participants were randomized?		Total study n.
How many participants were analyzed?		Total study n. If the numbers differ for different outcomes or time points, report the number of participants analyzed for the primary outcome. If not specified, use the **time of the first measurement**.

Supplementary File 2. Data Extraction Guide

Was a sample size calculation reported?	□Yes □ No	
If yes, what was the calculated sample size?		

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Consent and recruitment in pediatric research: an evaluation of trials published in 2012

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Title: Consent and recruitment in pediatric research: an evaluation of trials published in 2012

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ABSTRACT

Objectives. We evaluated 300 pediatric trials to determine: the consent and recruitment strategies used; how trial information was presented to families; how incentives were used; and if they achieved their recruitment targets.

Methods. For this cross-sectional evaluation, we searched the Cochrane Central Register of Controlled trials for pediatric trials published in 2012 and randomly selected 300 that reported on outcomes for participants aged ≤21 years. We collected data on consent and recruitment procedures for each trial and undertook descriptive analyses in SPSS Statistics.

Results. All but one trial (99.7%) used a standard recruitment strategy. Most (92%) trials reported that consent was obtained but only 13% reported who obtained consent. Two-thirds (65%) of trials included school-aged participants, and of these 68% reported obtaining assent. Half (50%) of the trials reported who the trial information was targeted to. Most trials (75%) of school-aged participants targeted information toward children or children and their parents. Fourteen percent of trials reported using incentives, half (50%) of which were in the form of compensation. Only 48% of trials reported sufficient data to determine if their recruitment targets were achieved. Of these, 70% achieved their targets.

Conclusions. Notable reporting shortcomings included: how families were recruited into the trial; who obtained consent and/or assent and how; who trial information was directed to; whether incentives were used; and sufficient data to determine if the recruitment target was achieved. Forthcoming pediatric-specific reporting standards may improve reporting in this priority area. Our data provide a baseline for ongoing monitoring of the state of the research.

WHAT IS KNOWN ABOUT THE SUBJECT

- In 2012, Standards for Research in (StaR) Child Health published evidence-based guidance to inform ethically-sound recruitment and consent in pediatric trials, and identified knowledge gaps.
- To optimize the value of children's participation in research, trialists must safeguard them from avoidable harm, use rigorous methodologies, and report their findings transparently.

WHAT THIS STUDY ADDS

- Reporting shortcomings included: how families were recruited; who obtained consent/assent; who trial information was directed to; whether incentives were used; if recruitment targets were reached.
- The data from this study will serve as a baseline for ongoing monitoring and evaluation of the state of the research.

INTRODUCTION

In 2012, Standards for Research in (StaR) Child Health published six evidence-based Standards to guide the rigorous design, conduct, and reporting of pediatric trials.[1, 2] Each Standard[3-8] includes practice recommendations and a research agenda to address knowledge gaps. To characterize the state of the literature, we analyzed a random sample of 300 pediatric trials published in 2012[9] and identified various shortcomings in their conduct and reporting. Among other issues, most trials reported results that were at unclear or high risk of bias, and only 46% were registered in a clinical trial registry.[9]

Trialists are ethically obligated to optimize the value of children's participation in research by safeguarding them from avoidable harms,[10, 11] using rigorous methodologies,[12] and reporting their findings transparently.[13] Ethically-sound recruitment and consent procedures include: obtaining consent from parents and assent from children; approaching all eligible children, and providing families with age-appropriate trial information; ensuring that incentives do not influence children's decision-making; and clearly differentiating between elements of standard care and those that are part of the trial.[3] Safeguarding children from avoidable harm also includes carefully planned recruitment targets. Trials that recruit too many participants needlessly expose children to the burdens of research participation, while those that are underpowered to detect clinically meaningful effects contribute to research waste.[14]

In response to the knowledge gaps and priorities identified by the Consent and Recruitment Standard Development Group, we evaluated the consent and recruitment procedures for 300 pediatric trials to determine: the consent and recruitment strategies used; the formats used to present trial information to families; how incentives were used; and whether they achieved their recruitment targets.

METHODS

Context

The analyses presented herein are part of a larger study[9, 15] in which we characterized the conduct and reporting qualities of 300 pediatric trials published in 2012. A full description of the study methods appears in a previous publication.[9]

Database search

In November 2013, we searched the Cochrane Central Register of Controlled Trials for randomized trials published in 2012 (Supplementary File 1). The Cochrane Central Register of Controlled Trials is a comprehensive database of reports of randomized and quasi-randomized trials, taken mainly from MEDLINE and Embase.[16] The 2012 publication date coincided with the publication of the StaR Child Health Standards.

Trial selection

We identified 2296 unique records via the search. We ordered these randomly in Excel (v. 2016; Microsoft Corporation, Redmond, Washington) and selected the first 300 published trials that reported on outcomes specific to participants ≤21 years of age (mean age at baseline). The sample size coincides with our previous evaluation of pediatric trials published in 2007.[15] We did not restrict our sample by language, condition, intervention, or outcome type.

Data extraction

For each included trial, we extracted data into REDCap (Research Electronic Data Capture)[17] pertaining to the characteristics of the: publication; trial design; intervention; trial conduct; trial sample; data monitoring committee and follow-up; outcomes and conclusions; risk of bias; and trial registration and protocol.[9] We also collected additional data to address the knowledge gaps and priorities outlined by the Standard Development Groups. An author (AG or MPD) verified the extracted data to identify errors or omissions.

Our data extraction guide for the variables included in this report is in Supplementary File 2. We classified the primary diagnostic category according to the World Health Organization's International Statistical Classification of Diseases and Related Health Problems 10th Revision.[18] We classified participants' recruitment location according to the World Bank income classification for the 2019 fiscal year.[19] We classified the recruitment strategy as standard if the participants provided consent and were then randomized in a typical manner (e.g., 1:1, 1:2). We classified the reasons for recruitment delays based on the definitions provided by Kaur et al.[20] We categorized incentives as one or more of the following: reimbursements (costs associated with participation that are paid back, e.g., parking, travel); compensation (participants are paid a modest amount for their time and effort); tokens of appreciation (a small gift given at the end of the trial, usually not known beforehand); and incentive payments (typically known before participation and used to enhance recruitment).

We referred to protocols, trial registries, and associated publications to complement data extraction. We searched for trial registers in the International Clinical Trials Registry Platform, the ISRCTN Registry, and via Google. We located trial registers for 46% (n = 138/300) of the trials.[9] We used protocols or companion articles only when cited in the publications. We did not contact authors to collect consent and recruitment details beyond those in published reports.

Data analysis

We exported the data to an Excel workbook for cleaning and to SPSS Statistics (v. 23; IBM Corporation, Armonk, New York) for descriptive analysis. We determined whether the recruitment target was reached by comparing the result of the sample size calculation to the number of participants enrolled in the trial.

RESULTS

Patient population and consent and recruitment procedures

Most trials recruited from high income countries[19] (n = 202/300, 67%) and 68% (n = 205/300) reported excluding patients with co-morbid or chronic diseases (Table 1). Only one trial (n = 1/300, 0.3%) reported using a non-standard recruitment strategy (Zelen's design). Only one trial (n = 1/300, 0.3%) reported a specified amount of time (seven days) for participants to decide whether to enroll. Seventeen percent (n = 51/300) of trials reported who first spoke to the family about participating. The most common point of contact was a researcher or clinician unknown to the participant (n = 28/51, 55%).

Most trials reported that consent was obtained (n = 275/300, 92%), but only 13% (n = 39/300) reported who obtained consent. Ninety percent (n = 270/300) of trials reported how consent was provided. Among these, 55% (n = 149/270) obtained consent via parental permission and 43% (n = 117/270) via parental permission combined with participant assent. Four trials (2%) reported only obtaining the consent of a mature minor. These included trials of the following: corrective exercises for scoliosis; prevention of acute knee injuries in athletes; bright-light therapy for non-seasonal depression; and oxidant and antioxidant levels in patients with orthodontic tooth movement. Of trials that included school-aged participants (>5 years old; n = 196/300, 65%), 68% (n =117/172) reported obtaining participant assent and 32% (n = 55/172) reported obtaining parental permission only. Three percent (n =

9/300) of trials reported that participants and families were involved in the design or conduct of the trial.

Nineteen percent (n = 56/300) of trials did not report the recruitment setting (or it was unclear). When clearly reported, most often trials recruited participants from inpatient populations (n = 74/300, 25%), outpatient populations (n = 51/300, 17%), or schools (n = 70/300, 23%).

Table 1. Characteristics of the patient populations and recruitment approaches (N = 300)

Characteristic	**n (%)**
Recruitment location*	
Low income country	16 (5.3)
Lower middle income country	33 (11.0)
Upper middle income country	56 (18.7)
High income country	202 (67.3)
Primary diagnostic category**	
Mental and behavioral disorders	50 (16.7)
Infectious and parasitic disease	39 (13.0)
Respiratory system	30 (10.0)
Conditions originating in the perinatal period	28 (9.3)
Endocrine, nutritional, and metabolic diseases	25 (8.3)
Oral health	19 (6.3)
Factors influencing health status and contact with health services	13 (4.3)
Digestive system	10 (3.3)
Blood, blood forming organs, and immune mechanism	7 (2.3)
Congenital malformations, deformations, and chromosomal abnormalities	7 (2.3)
Nervous system	7 (2.3)
Eye and adnexa	5 (1.7)
Ear and mastoid process	4 (1.3)
Injury, poisoning, and consequences of external causes	4 (1.3)
Circulatory system	3 (1.0)
External causes of morbidity and mortality	3 (1.0)
Genitourinary system	3 (1.0)
Musculoskeletal system and connective tissue	3 (1.0)
Neoplasms	3 (1.0)
Pregnancy, childbirth, and the puerperium	2 (0.7)
Skin and subcutaneous tissue	2 (0.7)
Other	33 (11.0)
Exclusion of patients with chronic diseases	
Yes	205 (68.3)
No	59 (19.7)
Unclear	36 (12.0)

Recruitment strategy	
Standard	299 (99.7)
Not standard	1 (0.3)
Time to decide whether to enroll	
Limited	1 (0.3)
Not reported	299 (99.7)
Who first approached the patient	
Child's clinician	8 (2.7)
Researcher or clinician unknown to patient	28 (9.3)
Other	15 (5.0)
Not reported	249 (83.0)
Consent obtained and reported	
Yes	275 (91.7)
No	25 (8.3)
Who obtained consent	
Child's clinician	2 (0.7)
Researcher or clinician unknown to patient	31 (10.3)
Other	6 (2.0)
Not reported	261 (87.0)
How consent was provided	
Parental permission	149 (49.7)
Parental permission and participant assent	117 (39.0)
Consent of a mature minor	4 (1.3)
Not reported	30 (10.0)
Patients/families involved in trial design/conduct	
Reported	9 (3.0)
Not reported	291 (97.0)
Source of recruitment* **	
Inpatients	74 (24.7)
Outpatients	51 (17.0)
Clinician's office	38 (12.7)
School	70 (23.3)
Community	44 (14.7)
Other	14 (4.7)
Unclear or not reported	56 (18.7)

*Defined according to the World Bank income classification, 2019 fiscal year.[19] Some trials recruited from more than one category.

**Defined according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (2010).[18] These data have been previously reported, but are shown here for context.[9]

***Total exceeds 300 because some trials reported multiple sources.

Formats used to present trial information to participants and families

About two-thirds (n = 184/300, 61%) of trials reported how families were informed about the opportunity to participate (Table 2). Of these, 59% (n = 108/184) reported that parents were

approached during a healthcare visit, 8% (n = 15/184) used mail invites, 4% (n = 7/184) approached parents by telephone, 14% (n = 26/184) used media messages (e.g., via the radio, newspaper, or a website), and 11% (n = 20/184) used pamphlets. Other methods (n = 63/184, 34%) included schools (i.e., school staff contacted parents about the trial), community contacts and word of mouth; and identifying potential participants through chart reviews or previous trials. Sixteen percent (n = 30/184) of trials used multiple means of informing families about the opportunity to participate.

Half (n = 151/300, 50%) of the trials reported the person who was the target of the trial information. Of these, 58% (n = 88/151) targeted the information toward parents, 37% (n = 56/151) toward parents and children, and 5% (n = 7/151) toward children only. Although it was not reported, we assumed that an additional 13% (n = 40/300) intended the information to be for parents, as participants were infants or children less than school age. When it was reported, all trials that included only participants ≤5 years of age directed the information to parents only (n = 64/64, 100%). Most trials (n = 65/87, 75%) that included participants >5 years of age directed trial information either to children or both parents and children. All of the trials (n = 5/5, 100%) in which information was directed specifically toward children were conducted in adolescents.

Table 2. Formats used to present trial information to participants and families (N = 300)

Characteristic	**n (%)**
How the family heard about the trial*	
Approached during healthcare visit	108 (36.0)
Mailing	15 (5.0)
Generalized mailing	4 (1.3)
Targeted mailing	9 (3.0)
Personalized mailing	2 (0.7)
Phone calls	7 (2.3)
Media	26 (8.7)
Pamphlets	20 (6.7)
Other	63 (21.0)
Not reported	116 (38.7)
Who trial information was targeted to	
Parents	88 (29.3)
Children	7 (2.3)
Parents and children	56 (18.7)
Not reported	149 (49.7)

*Some trials used multiple approaches.

Use of incentives

Most trials did not report whether incentives were used (n = 253/300, 84%) and five (2%) reported not using incentives. Fourteen percent (n = 42/300) of trials reported using incentives. These were most often in the form of compensation (n = 21/42, 50%) and tokens of appreciation (n = 12/42, 29%) (five studies (12%) provided reimbursements and seven (17%) provided incentive payments). Reported compensation amounts varied, e.g., free dental care and $20 for families participating in a 5-year dental amalgam trial; $5 to $10 gift cards for adolescents participating in a trial of telephone-based preventive health education and counseling. Tokens of appreciation also varied, e.g., an insecticide impregnated bed net and soap for families participating in a trial of therapeutic food for catch-up growth after malaria; $40 for teachers participating in a trial of a school-based intervention. Tables 3 and 4 show the reported incentive use and types of incentives used stratified by continent of recruitment. The use of incentives was most often reported in studies that recruited from North America (n = 33/119, 28%). All studies that offered incentive payments recruited from North America.

The child was often the recipient of the incentive, rather than the parents or family: 20% (n =1/5) of reimbursements (e.g., $5 for a bus ticket for travel), 48% (n = 10/21) of compensation incentives (e.g., $10 for completing a survey), 50% (n = 6/12) of tokens of appreciation (e.g., $10 gift certificate), and 83% (n = 5/6) of incentive payments (e.g., $50 supermarket gift cards) were intended for the participant.

Table 3. Use of incentives stratified by recruitment continent (N = 300)*

Recruitment continent	N	Use of incentives, n (%)		
		Yes	No	Not reported
Africa	26	3 (11.5)	1 (3.8)	22 (84.6)
Asia	82	1 (1.2)	2 (2.4)	79 (96.3)
Australia	18	3 (16.7)	0 (0.0)	15 (83.3)
Europe	54	2 (3.7)	3 (5.6)	49 (90.7)
North America	119	33 (27.7)	0 (0.0)	86 (72.3)
South America	9	0 (0.0)	0 (0.0)	9 (100.0)

*Some studies recruited participants from more than one continent.

Table 4. Types of incentives used stratified by continent (N = 42)*

Recruitment continent	N	Types of incentives used, n (%)			
		Reimbursements	Compensation	Tokens of appreciation	Payments
Africa	3	1 (33.3)	2 (66.7)	1 (33.3)	0 (0.0)
Asia	1	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
Australia	3	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)
Europe	2	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)
North America	33	2 (6.1)	16 (48.5)	10 (30.3)	7 (21.2)

South America	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*Some studies offered multiple types of incentives.

Recruitment target attainment

About half (n = 145/300, 48%) of the trials reported sufficient information to determine if the recruitment target was achieved (Table 5). Of these, 70% (n = 102/145) recruited their target sample size. Recruitment delays were reported in 6% (n = 19/300) of trials, and were most often due to patient level (n = 10/19, 53%; e.g., travel, duration of trial, preferences) or trial level factors (n = 9/19, 47%; e.g., funding, trial management, feasibility). Strategies to address recruitment delays included stopping the trial before the recruitment target was achieved (n = 13/19, 68%), extending the recruitment period (n = 3/19, 16%), adding trial sites (n = 2/19, 11%), modifying the eligibility criteria (n = 3/19, 16%), and modifying the incentives (n = 1/19, 5%).

Table 5. Recruitment target attainment (N = 300)

Characteristic	**n (%)**
Sample size	
Calculation reported	155 (51.7)
Recruitment target reached*	102/145 (70.3)
Recruitment delays reported	
Yes	19 (6.3)
No	281 (93.7)
Types of recruitment delays**	
Trial level factors	9/19 (47.4)
Site level factors	1/19 (5.3)
Patient level factors	10/19 (52.6)
Trial team level factors	1/19 (5.3)
Not specified	4/19 (21.1)
How recruitment delays were addressed***	
Extending the recruitment period	3/19 (15.8)
Adding additional trial sites	2/19 (10.5)
Modifying the eligibility criteria	3/19 (15.8)
Modifying incentives	1/19 (5.3)
Stopping the trial before reaching the target	13/19 (68.4)

*Based on sample size calculation and number randomized; data for this calculation were unavailable for 10 trials that reported a sample size calculation.
**Total exceeds 19 because some trials reported more than one type of delay.
***Total exceeds 19 because some trials reported more than one method.

DISCUSSION

This study addresses some of the knowledge gaps and priorities identified by StaR Child Health's Consent and Recruitment Standard Development Group.[3] We found that details of consent and

recruitment procedures were infrequently reported within publications of pediatric trials. Although most trials reported obtaining consent, elaboration on the consent and recruitment process was not common.

Despite being widely accepted as a requirement,[11, 21] there remains ambiguity about what constitutes assent in pediatric trials,[22] which children are capable of providing it,[22] and how it should be reported.[23] Recently, Tait and Geisser (2017) established an operational definition of assent, including recommendations about the level of information appropriate for different ages.[24] Nevertheless, guidance on the age at which children must provide assent varies substantially by country.[25-27] It also remains unclear whether the level of detail regarding consent and recruitment procedures required by research ethics boards is appropriate or necessary in published reports of pediatric trials. In 2010, Saint-Raymond et al. called attention to the need for reporting guidelines specific to research with children.[23] The development of pediatric adaptations of the Standard Protocol Items: Recommendations for Interventional Trials[28] and Consolidated Standards of Reporting Trials[29] statements is underway.[30]

Fewer than 20% of trials reported who approached families to participate. Although a relationship to the person obtaining consent can encourage recruitment,[31] when the person is the child's healthcare provider parents may worry that refusing participation will impact their child's quality of care.[22] In most trials of school-aged children, trial information was directed to both parents and children. Parents' and children's understanding of trial materials are fundamental to ethical and efficient recruitment.[3] Not understanding trial information discourages parents and children from enrolling in trials,[31] and typical presentations of the benefits and risks of trial participation are often difficult for parents to understand.[32] The integrated consent model in which clinicians engage the trial participant in a consent conversation similar to usual care and additionally present the opportunity for the randomization of previously validated treatment options, has been proposed.[33] This approach has been suggested for low-risk and pragmatic trials,[33] however the applicability to pediatric trials needs to be established.

Few trials reported whether incentives were used, but of those that did, many were intended for children. Trial participation can be costly for families, and there is general consensus that they should be reimbursed for the related expenses (e.g., travel, parking) at a rate that is sufficient but does not lead them to undervalue risks or coerce them to consent.[22, 31] As children value incentives differently than adults, their provision to minors is controversial.[3, 10] When incentives are used, it is critical that children

understand the implications of the trial and that the incentives do not influence their decision to participate.[3, 10]

Seventy percent of trials met their recruitment targets. This is substantially greater than the 29% reported in St-Louis et al.'s review of pediatric general surgical trials,[34] and the 55% in Sully et al.'s review of multicenter trials in the United Kingdom.[35] Failing to meet the recruitment target contributes to research waste when the trial is underpowered to detect clinically important differences.[36] Due to reporting deficiencies, we could only ascertain whether trials achieved their recruitment targets for half of the sample. Whether transparent reporting is biased toward trials that meet their recruitment targets is not yet known.

Strengths and Limitations

We have highlighted a number of conduct and/or reporting gaps in an effort to contribute to the ongoing research agenda. Our sample will serve as a baseline for ongoing monitoring of consent and recruitment procedures in pediatric trials. The extracted data were limited to those available within published reports, therefore we cannot ascertain the extent to which the findings reflect conduct and/or reporting shortcomings. We used a sample of trials published in 2012, and the findings may not be generalizable to other years.

CONCLUSIONS

In our sample, five reporting shortcomings were evident: how families were recruited; who obtained consent and/or assent and how; who trial information was directed to; whether incentives were used; and sufficient data to determine if the recruitment target was met. Forthcoming reporting guidance specific to pediatric trials[30] and the StaR Child Health Standards[3] may contribute to improving the conduct and reporting of pediatric trials in this priority area. Using this study as a baseline, continued monitoring of the state of the research will allow for the identification of changes over time and the need for knowledge translation.

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COMPETING INTERESTS

We have no financial or other conflicts of interest to declare.

CONTRIBUTORS' STATEMENT

Dr Dyson conceptualized the study, designed the data collection instrument, supervised all aspects of the work, verified and analyzed the extracted data, and contributed to drafting the manuscript.
Dr Gates verified and analyzed the extracted data, contributed to drafting the manuscript, and completed revisions of the manuscript drafts following input from the other authors.
Drs Caldwell, Curtis, Dans, Hartling, Kelly, Fernandes, Woolfall, and Williams contributed to the interpretation of the extracted data, and revised manuscript drafts critically for important intellectual content.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DATA SHARING STATEMENT

The data collected and analyzed from trials included in this study will be available to researchers via reasonable request from the corresponding author. The data will be available immediately following, and for 5 years after article publication. Our data extraction guide is available as a supplementary file.

PREVIOUS PRESENTATION

Parts of this research were presented as a poster at our local research day (Pediatric Research Day, Department of Pediatrics, University of Alberta, Edmonton, Canada) on 16 May 2018 under the

following title: “The safe and ethical participation of children in research: a descriptive analysis of the conduct and reporting of trials published in 2012”.

REFERENCES

1. Wittmeier KD, Craig J, Klassen TP, et al. The mission of StaR Child Health is to improve the quality of the design, conduct, and reporting of pediatric clinical research by promoting the use of modern research standards. Introduction. *Pediatrics* 2012;129(Suppl 3):S111.
2. 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):S112-17.
3. Caldwell PH, Dans L, de Vries MC, et al. Standard 1: consent and recruitment. *Pediatrics* 2012;129(Suppl 3):S118-23.
4. Ellenberg S, Fernandes RM, Saloojee H, et al. Standard 3: data monitoring committees. *Pediatrics* 2012;129(Suppl 3):S132-7.
5. Hartling L, Hamm M, Klassen T, et al. Standard 2: containing risk of bias. *Pediatrics* 2012;129(Suppl 3):S124-31.
6. 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):S146-52.
7. van der Tweel I, Askie L, Vandermeer B, et al. Standard 4: determining adequate sample sizes. *Pediatrics* 2012;129(Suppl 3):S138-45.
8. Williams K, Thomson D, Seto I, et al. Standard 6: age groups for pediatric trials. *Pediatrics* 2012;129(Suppl 3):S153-60.
9. 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.
10. Joseph PD, Craig JC, Caldwell PH. Clinical trials in children. *Br J Clin Pharmacol* 2015;79(3):357-69.
11. Graham A, Powell M, Taylor N, et al. Ethical research involving children: putting the evidence into practice. *Family Matters* 2015;96:23-8.
12. Ioannidis JP, Greenland S, Hlatky MA, et al. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet* 2014;383:166-75.

13. Glasziou P, Altman DG, Bossuyt P, et al. Reducing waste from incomplete or unusable reports of biomedical research. *Lancet* 2014;383:267-76.
14. Nayak BK. Understanding the relevance of sample size calculation. *Indian J Ophthalmol* 2010;58:469.
15. 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.
16. Cochrane. Cochrane Central Register of Controlled Trials (CENTRAL). London, United Kingdom: Cochrane. c1999-2018. Available from: http://www.cochranelibrary.com/about/central-landing-page.html. Accessed 5 September 2018.
17. 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.
18. World Health Organization. Classifications. International Classification of Diseases (ICD). ICD-10 online versions. Geneva, Switzerland: World Health Organization. 2018. Available from: http://www.who.int/classifications/icd/icdonlineversions/en/. Accessed 5 September 2018.
19. The World Bank. World Bank Country and Lending Groups. Washington, District of Columbia: The World Bank. 2018. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. Accessed 11 September 2018.
20. Kaur G, Smyth RL, Williamson P. Developing a survey of barriers and facilitators to recruitment in randomized controlled trials. *Trials* 2012;13:218.
21. General Assembly of the World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191-4.
22. Leibson T, Koren G. Informed consent in pediatric research. *Paediatr Drugs* 2015;17:5-11.
23. Saint-Raymond A, Hill S, Martines J, et al. CONSORT 2010. *Lancet* 2010;376(9737):229-30.
24. Tait AR, Geisser ME. Development of a consensus operational definition of child assent for research. *BMC Med Ethics* 2017;18:41.
25. Shaddy RE, Denne SC, The Committee on Drugs and Committee on Pediatric Research. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Pediatrics* 2010;125:850-60. Reaffirmed January 2014; 133:e1479.
26. Lepola P, Needham A, Mendum J, et al. Informed consent for paediatric clinical trials in Europe. *Arch Dis Child*. 2016;101:1017-25.

27. Canadian Paediatric Society. Ethical issues in health research in children. *Paediatr Child Health* 2008;13:707-20.
28. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200-7.
29. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Trials* 2010;11:32.
30. Clyburne-Sherin AVP, Thurairajah P, Kapadia MZ, et al. Recommendations and evidence for reporting items in pediatric clinical trial protocols and reports: two systematic reviews. *Trials* 2015;16:417.
31. Tromp K, Zwaan CM, van de Vathorst S. Motivations of children and their parents to participate in drug research: a systematic review. *Eur J Pediatr* 2016;175:599-12.
32. Tait AR, Voepel-Lewis T, Zikmund-Fisher BJ, et al. Presenting research risks and benefits to parents: does format matter? *Anesth Analg* 2010;111:718-23.
33. Kim SY, Miller FG. Informed consent for pragmatic trials: the integrated consent model. *NEJM* 2014;370:769-72.
34. St-Louis E, Oosenbrug M, Landry T, et al. Enrollment and reporting practices in pediatric general surgical randomized clinical trials: a systematic review and observational analysis. *J Pediatr Surg* 2018;53:879-84.
35. Sully BG, Julious SA, Nicholl J. A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies. *Trials* 2013;14:166.
36. Salman RA-S, Beller E, Kagan J, Hemminki E, et al. Increasing value and reducing waste in biomedical research regulation and management. *Lancet* 2014;383:176-85.

Supplementary File 1. Search Strategy

Summary of Search

Database	Date Searched	Number Retrieved	After Duplicate Removal
Cochrane Central Register of Controlled Trials (Wiley)	November 4, 2013	2343	2296
Total		**2343**	**2296**

Database: Cochrane Central Register of Controlled Trials (Wiley)

Date Searched: 4 November 2013 at 21:07:57.057

Results: 2343 records (2296 following duplicate removal)

Search Strategy:

#1 (Infant* or infancy or Newborn* or Baby* or Babies or Neonat* or Preterm* or Prematur* or Postmatur* or Child* or Schoolchild* or School age* or Preschool* or Kid or kids or Toddler* or Teen* or Boy* or Girl* or Minors* or Pubert* or Pubescen* or Prepubescen* or Pediatric* or Paediatric* or Peadiatric* or Nursery school* or Kindergar* or Primary school* or Secondary school* or Elementary school* or High school* or Highschool*):ti,ab,kw

#2 (Adolesc*):ti,ab

#3 (Infant or Child or Minors or Puberty or Pediatrics or Schools):kw

#4 #1 or #2 or #3

#5 adolescent*:kw

#6 (adolescent* and (adult* or elderly or "middle aged" or "aged, 80 and over")):kw

#7 #6 and not #4

#8 #4 or #5

#9 #8 and not #7 from 2012 to 2012, in Trials

Supplementary File 2. Data Extraction Guide

Field	Response	Comments
Trial conduct		
Where were participants recruited from?	□Low income country □Lower middle income country □Upper middle income country □High income country	Select all that apply. Classified according to the World Bank income classifications, 2019 fiscal year. Expressed as GNI per capita: **Low income country:** <$995/year **Lower middle income country:** $996 to $3895/year **Upper middle income country:** $3896 to $$12055/year **High income country:** ≥$12056/year https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups
What recruitment strategies were used?	□Standard □Not standard	**Standard:** Participants provide consent and then are randomized in a typical 1:1, 1:2, etc. manner. **Not standard:** Any of: – Open trial design (randomization occurs before participants are approached, so that participants are informed of the treatment they were randomized to receive prior to consent) – Increasing or decreasing the chance of receiving the experimental treatment – Experimental treatment for all participants and standard treatment for non-participants – Standard care for all participants and experimental treatment for non-participants – Random assignment of treatment for participants and choice of treatment for non-participants – Opt in or opt out recruitment (consent was sought for participation or non-participation)
Who first approached the patient about participating in the trial?	□Child's clinician □Researcher/clinician unknown to patient □Other (specify): □Not reported	Other professionals could include individuals such as teachers.
How did the family first	□Approached during healthcare	Select all that apply.

Supplementary File 2. Data Extraction Guide

hear about the trial?	visit □Generalized mailing □Targeted mailing □Personalized mailing □Phone calls □Media □Pamphlets □Not reported □Other (specify):	**Generalized mailing:** mail out to a large population **Targeted mailing:** mail out to a targeted group **Personalized mailing:** mailing addressed to the individual **Media:** Internet, newspaper, radio, TV **Pamphlets:** given to the families or left out for participants to pick up
Who was the trial information targeted to?	□Parents □Children □Both □Not reported	"Trial information" refers to recruitment materials.
Did the authors report that consent was obtained?	□Yes □No	
If yes, who obtained consent from the participants?	□Child's clinician □Researcher/clinician unknown to patient □Other (specify): □Not reported	Other professionals could include individuals such as teachers.
If yes, how was consent provided in the study?	□Parental permission □Parental permission and participant assent □Consent of a mature minor □N/A	Can assume parental consent if consent reported but not specified, and no other indication that another model was used.
Were any incentives used in the study?	□Yes □No □Not reported	
If yes, what incentives were used?	□Reimbursement □Parents □Child □Families (no other detail) □Not reported □Compensation □Parents	Select all that apply. **Reimbursement:** costs associated with participation in the study (e.g., travel, parking) are paid back. **Compensation:** participants are paid a modest amount for their time/effort. **Appreciation:** a small token gift given at the end of the study, usually not known beforehand.

Supplementary File 2. Data Extraction Guide

	□Child □Families (no other detail) □Not reported □Appreciation □Parents □Child □Families (no other detail) □Not reported □Payment □Parents □Child □Families (no other detail) □Not reported □N/A	**Payment:** typically known before study participation and used as a strategy to enhance recruitment. *Use "families" only if specified as such in the publication, with no information provided on whether the incentives were meant for the parents or child.
How long were participants given to decide whether or not to enroll in the trial?	□No restriction □Limited □No time □Not reported	**No restriction:** hours to weeks **Limited:** immediately to less than a few hours **No time:** retrospective consent
Were any delays, shortfalls, or difficulties in recruitment reported once the trial was underway?	□Yes □No	
If yes, what were the reasons for the delays or difficulties?	□Trial level factors □Site level factors □Patient level factors □Clinical team level factors □Information and consent factors □Study team level factors □Other (specify): □N/A	Examples (for more detail, see *Kaur Trials 2012*): **Trial level:** funding, trial management, feasibility **Site level:** competing projects, time to open up site **Patient level:** travel, costs, duration of trial and follow-up, preferences, language or cultural barrier **Information and consent:** amount and complexity of trial information provided, experience of clinical team seeking consent **Study team level:** experience and training of team, clinical workload, clinician attitude towards research or treatment
How were the recruitment delays or difficulties addressed?	□Described (specify): □Not described □No difficulties	
Was the use of patient or	□Yes (specify):	For involvement in the **conduct** of the study, consider involvement past the

Supplementary File 2. Data Extraction Guide

family involvement in the design or conduct of the study reported?	□No	point where a decision is made to participate, i.e., the participant/family has already enrolled prior to the involvement referred to.
How was the study population selected?	□Inpatients □NICU □PICU □Not reported □Other (specify): □Outpatients □Clinicians' office □School □Community □Unclear □Other (specify):	Select all that apply. In the case of selection from a dental clinic, report "Doctor's office."
What primary diagnostic category was involved in the study?	□Infectious and parasitic diseases □Neoplasms □Blood, blood forming organs, and immune mechanism □Endocrine, nutritional, and metabolic diseases □Mental and behavioural disorders □Nervous system □Eye and adnexa □Ear and mastoid process □Circulatory system □Respiratory system □Digestive system □Skin and subcutaneous tissue □Musculoskeletal system and connective tissue □Genitourinary system □Pregnancy, childbirth, and the puerperium □Conditions originating in the	Select the primary diagnostic category of the study using the ICD-10 classification system. *(ICD-10 Version:2010* *http://apps.who.int/classifications/icd10/browse/2010/en)*

Supplementary File 2. Data Extraction Guide

	perinatal period □Congenital malformations, deformations, and chromosomal abnormalities □Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified □Injury, poisoning, and consequences of external causes □External causes of morbidity and mortality □Factors influencing health status and contact with health services □Oral health □Other (specify):	
Did the study exclude participants who had at least one chronic condition (other than the condition that was the focus of the trial) or a co-morbid condition?	□Yes □No □Unclear	
Sample size		
How many patients were approached to participate in the study?		Use NR if applicable.
How many patients consented to participate in the study?		Use NR if applicable. *This is not necessarily the same number as randomized.
How many participants were randomized?		Total study n.
How many participants were analyzed?		Total study n. If the numbers differ for different outcomes or time points, report the number of participants analyzed for the primary outcome. If not specified,

Supplementary File 2. Data Extraction Guide

		use the **time of the first measurement**.
Was a sample size calculation reported?	□Yes □ No	
If yes, what was the calculated sample size?		

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ABSTRACT

Objectives. We evaluated 300 pediatric trials to determine: the consent and recruitment strategies used; who trial information was targeted to; how incentives were used; and if they achieved their recruitment targets.

Methods. For this cross-sectional evaluation, we searched the Cochrane Central Register of Controlled trials for pediatric trials published in 2012 and randomly selected 300 that reported on outcomes for participants aged ≤21 years. We collected data on consent and recruitment procedures for each trial and undertook descriptive analyses in SPSS Statistics.

Results. All but one trial (99.7%) used a standard recruitment strategy. Most (92%) trials reported that consent was obtained but only 13% reported who obtained consent. Two-thirds (65%) of trials included school-aged participants, and of these 68% reported obtaining assent. Half (50%) of the trials reported who the trial information was targeted to. Most trials (75%) of school-aged participants targeted information toward children or children and their parents. Fourteen percent of trials reported using incentives, half (50%) of which were in the form of compensation. Only 48% of trials reported sufficient data to determine if their recruitment targets were achieved. Of these, 70% achieved their targets.

Conclusions. Notable reporting shortcomings included: how families were recruited into the trial; who obtained consent and/or assent and how; who trial information was directed to; whether incentives were used; and sufficient data to determine if the recruitment target was achieved. Forthcoming pediatric-specific reporting standards may improve reporting in this priority area. Our data provide a baseline for ongoing monitoring of the state of the research.

WHAT IS KNOWN ABOUT THE SUBJECT

- In 2012, Standards for Research in (StaR) Child Health published evidence-based guidance to inform ethically-sound recruitment and consent in pediatric trials, and identified knowledge gaps.
- To optimize the value of children's participation in research, trialists must safeguard them from avoidable harm, use rigorous methodologies, and report their findings transparently.

WHAT THIS STUDY ADDS

- Reporting shortcomings included: how families were recruited; who obtained consent/assent; who trial information was directed to; whether incentives were used; if recruitment targets were reached.
- The data from this study will serve as a baseline for ongoing monitoring and evaluation of the state of the research.

INTRODUCTION

In 2012, Standards for Research in (StaR) Child Health published six evidence-based Standards to guide the rigorous design, conduct, and reporting of pediatric trials.[1, 2] Each Standard[3-8] includes practice recommendations and a research agenda to address knowledge gaps. To characterize the state of the literature, we analyzed a random sample of 300 pediatric trials published in 2012[9] and identified various shortcomings in their conduct and reporting. Among other issues, most trials reported results that were at unclear or high risk of bias, and only 46% were registered in a clinical trial registry.[9]

Trialists are ethically obligated to optimize the value of children's participation in research by safeguarding them from avoidable harms,[10, 11] using rigorous methodologies,[12] and reporting their findings transparently.[13] Ethically-sound recruitment and consent procedures include: obtaining consent from parents and assent from children; approaching all eligible children and not unfairly excluding any children; providing families with age-appropriate trial information; ensuring that incentives do not influence children's decision-making; and clearly differentiating between elements of standard care and those that are part of the trial.[3] Safeguarding children from avoidable harm also includes carefully planned recruitment targets. Trials that recruit too many participants needlessly expose children to the burdens of research participation, while those that are underpowered to detect clinically meaningful effects contribute to research waste.[14]

In response to the knowledge gaps and priorities identified by the Consent and Recruitment Standard Development Group, we evaluated the consent and recruitment procedures for 300 pediatric trials to determine: the consent and recruitment strategies used; who trial information was targeted to; how incentives were used; and whether they achieved their recruitment targets.

METHODS

Context

The analyses presented herein are part of a larger study[9, 15] in which we characterized the conduct and reporting qualities of 300 pediatric trials published in 2012. A full description of the study methods appears in a previous publication.[9]

Database search

In November 2013, a research librarian searched the Cochrane Central Register of Controlled Trials (CENTRAL) for randomized trials published in 2012 (Supplementary File 1). CENTRAL is a comprehensive database of reports of randomized and quasi-randomized trials, taken mainly from MEDLINE and Embase.[16] The 2012 publication date coincided with the publication of the StaR Child Health Standards.

Trial selection

2296 unique records were identified via the search. We ordered these randomly in Excel (v. 2016; Microsoft Corporation, Redmond, Washington) and selected the first 300 published trials that: (a) recruited participants aged 0 to 18 years, or (b) recruited both children and adults with an upper age limit of 21 years. The inclusion criteria were selected to match those used by Cochrane Child Health to select trials for their Trials Register (which originate from CENTRAL).[17] The sample size coincides with our previous evaluation of pediatric trials published in 2007.[15] The sample was not restricted by language, condition, intervention, or outcome type.

Data extraction

For each included trial, we extracted data into REDCap (Research Electronic Data Capture)[18] pertaining to the characteristics of the: publication; trial design; intervention; trial conduct; trial sample; data monitoring committee and follow-up; outcomes and conclusions; risk of bias; and trial registration and protocol.[9] We also collected additional data to address the knowledge gaps and priorities outlined by the Standard Development Groups. An author (AG or MPD) verified the extracted data to identify errors or omissions.

The data extraction guide for the variables included in this report is in Supplementary File 2. The primary diagnostic category was classified according to the World Health Organization's International Statistical Classification of Diseases and Related Health Problems 10th Revision.[19] Participants' recruitment location was classified according to the World Bank income classification for the 2019 fiscal year.[20] The recruitment strategy was classified as standard if the participants provided consent and were then randomized in a typical manner (e.g., 1:1, 1:2). The reasons for recruitment delays were classified based on the definitions provided by Kaur et al.[21] Incentives were categorized as one or more of the following: reimbursements (costs associated with participation that are paid back, e.g., parking, travel); compensation (participants are paid a modest amount for their time and effort); tokens of appreciation (a small gift given at the end of the trial, usually not known beforehand); and incentive payments (typically known before participation

and used to enhance recruitment). Children were considered to be of "school age" if they were >5 years old. Participants were considered "mature minors" if they were adolescents or young adults aged ≥12 years. Whether children with chronic or co-morbid conditions were excluded was collected to estimate if children were fairly and equitably recruited into the trial.

We referred to protocols, trial registries, and associated publications to complement data extraction. Trial registers were sought via the International Clinical Trials Registry Platform, the ISRCTN Registry, and Google. Trial registers were located for 46% (n = 138/300) of the trials.[9] Protocols or companion articles were used only when cited in the publications. Authors were not contacted to collect consent and recruitment details beyond those in published reports.

Data analysis

The data were exported to an Excel workbook for cleaning and to SPSS Statistics (v. 23; IBM Corporation, Armonk, New York) for descriptive analysis. To determine whether the recruitment target was reached, the result of the sample size calculation was compared to the number of participants enrolled in the trial. The data on the use of incentives were stratified by continent because allowable incentives for pediatric research vary by region (e.g., the European Union advocates banning all incentive payments for children, while incentive payments for children participating in trials are relatively common in the United States).[10]

RESULTS

Patient population and consent and recruitment procedures

Most trials recruited from high income countries[20] (n = 202/300, 67%) and 68% (n = 205/300) reported excluding patients with co-morbid or chronic diseases (Table 1). Only one trial (n = 1/300, 0.3%) reported using a non-standard recruitment strategy (Zelen's design, whereby participants are randomly allocated to treatment before seeking consent; participants can accept or decline the intervention offered). Only one trial (n = 1/300, 0.3%) reported a specified amount of time (seven days) for participants to decide whether to enroll. Seventeen percent (n = 51/300) of trials reported who first spoke to the family about participating. The most common point of contact was a researcher or clinician unknown to the participant (n = 28/51, 55%).

Most trials reported that consent was obtained (n = 275/300, 92%), but only 13% (n = 39/300) reported who obtained consent. Ninety percent (n = 270/300) of trials reported how consent was provided. Among

these, 55% (n = 149/270) obtained consent via parental permission and 43% (n = 117/270) via parental permission combined with participant assent. Four trials (2%) reported only obtaining the consent of a mature minor. These included trials of the following: corrective exercises for scoliosis; prevention of acute knee injuries in athletes; bright-light therapy for non-seasonal depression; and oxidant and antioxidant levels in patients with orthodontic tooth movement. Of trials that included school-aged participants (>5 years old; n = 196/300, 65%), 68% (n =117/172) reported obtaining participant assent and 32% (n = 55/172) reported obtaining parental permission only. Three percent (n = 9/300) of trials reported that participants and families were involved in the design or conduct of the trial.

Nineteen percent (n = 56/300) of trials did not report the recruitment setting (or it was unclear). When clearly reported, most often trials recruited participants from inpatient populations (n = 74/300, 25%), outpatient populations (n = 51/300, 17%), or schools (n = 70/300, 23%).

Table 1. Characteristics of the patient populations and recruitment approaches (N = 300)

Characteristic	**n (%)**
Recruitment location*	
Low income country	16 (5.3)
Lower middle income country	33 (11.0)
Upper middle income country	56 (18.7)
High income country	202 (67.3)
Exclusion of patients with chronic diseases	
Yes	205 (68.3)
No	59 (19.7)
Unclear	36 (12.0)
Recruitment strategy	
Standard	299 (99.7)
Not standard	1 (0.3)
Time to decide whether to enroll	
Limited	1 (0.3)
Not reported	299 (99.7)
Who first approached the patient	
Child's clinician	8 (2.7)
Researcher or clinician unknown to patient	28 (9.3)
Other	15 (5.0)
Not reported	249 (83.0)
Consent obtained and reported	
Yes	275 (91.7)
No	25 (8.3)
Who obtained consent	
Child's clinician	2 (0.7)

Researcher or clinician unknown to patient	31 (10.3)
Other	6 (2.0)
Not reported	261 (87.0)
How consent was provided	
Parental permission	149 (49.7)
Parental permission and participant assent	117 (39.0)
Consent of a mature minor	4 (1.3)
Not reported	30 (10.0)
Patients/families involved in trial design/conduct	
Reported	9 (3.0)
Not reported	291 (97.0)
Source of recruitment**	
Inpatients	74 (24.7)
Outpatients	51 (17.0)
Clinician's office	38 (12.7)
School	70 (23.3)
Community	44 (14.7)
Other	14 (4.7)
Unclear or not reported	56 (18.7)
Primary diagnostic category***	
Mental and behavioral disorders	50 (16.7)
Infectious and parasitic disease	39 (13.0)
Respiratory system	30 (10.0)
Conditions originating in the perinatal period	28 (9.3)
Endocrine, nutritional, and metabolic diseases	25 (8.3)
Oral health	19 (6.3)
Factors influencing health status and contact with health services	13 (4.3)
Digestive system	10 (3.3)
Blood, blood forming organs, and immune mechanism	7 (2.3)
Congenital malformations, deformations, and chromosomal abnormalities	7 (2.3)
Nervous system	7 (2.3)
Eye and adnexa	5 (1.7)
Ear and mastoid process	4 (1.3)
Injury, poisoning, and consequences of external causes	4 (1.3)
Circulatory system	3 (1.0)
External causes of morbidity and mortality	3 (1.0)
Genitourinary system	3 (1.0)
Musculoskeletal system and connective tissue	3 (1.0)
Neoplasms	3 (1.0)
Pregnancy, childbirth, and the puerperium	2 (0.7)
Skin and subcutaneous tissue	2 (0.7)
Other	33 (11.0)

*Defined according to the World Bank income classification, 2019 fiscal year.[20] Some trials recruited from more than one category.

**Total exceeds 300 because some trials reported multiple sources.
***Defined according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (2010).[18] These data have been previously reported, but are shown here for context.[9]

Who trial information was targeted to

About two-thirds (n = 184/300, 61%) of trials reported how families were informed about the opportunity to participate (Table 2). Of these, 59% (n = 108/184) reported that parents were approached during a healthcare visit, 8% (n = 15/184) used mail invites, 4% (n = 7/184) approached parents by telephone, 14% (n = 26/184) used media messages (e.g., via the radio, newspaper, or a website), and 11% (n = 20/184) used pamphlets. Other methods (n = 63/184, 34%) included schools (i.e., school staff contacted parents about the trial), community contacts and word of mouth; and identifying potential participants through chart reviews or previous trials. Sixteen percent (n = 30/184) of trials used multiple means of informing families about the opportunity to participate.

Half (n = 151/300, 50%) of the trials reported the person who was the target of the trial information. Of these, 58% (n = 88/151) targeted the information toward parents only, 5% (n = 7/151) toward mature minors only, and 37% (n = 56/151) toward parents and children. Although it was not reported, we assumed that an additional 13% (n = 40/300) intended the information to be for parents, as participants were infants or children less than school age. When it was reported, all trials that included only participants ≤5 years of age directed the information to parents only (n = 64/64, 100%). Most trials (n = 65/87, 75%) that included participants >5 years of age directed trial information either to mature minors only or both parents and children.

Table 2. Formats used to present trial information to participants and families (N = 300)

Characteristic	**n (%)**
How the family heard about the trial*	
Approached during healthcare visit	108 (36.0)
Mailing	15 (5.0)
Generalized mailing	4 (1.3)
Targeted mailing	9 (3.0)
Personalized mailing	2 (0.7)
Phone calls	7 (2.3)
Media	26 (8.7)
Pamphlets	20 (6.7)
Other	63 (21.0)

Not reported	116 (38.7)
Who trial information was targeted to	
Parents	88 (29.3)
Mature minors	7 (2.3)
Parents and children	56 (18.7)
Not reported	149 (49.7)

*Some trials used multiple approaches.

Use of incentives

Most trials did not report whether incentives were used (n = 253/300, 84%) and five (2%) reported not using incentives. Fourteen percent (n = 42/300) of trials reported using incentives. These were most often in the form of compensation (n = 21/42, 50%) and tokens of appreciation (n = 12/42, 29%) (five studies (12%) provided reimbursements and seven (17%) provided incentive payments). Reported compensation amounts varied, e.g., free dental care and $20 for families participating in a 5-year dental amalgam trial; $5 to $10 gift cards for adolescents participating in a trial of telephone-based preventive health education and counseling. Tokens of appreciation also varied, e.g., an insecticide impregnated bed net and soap for families participating in a trial of therapeutic food for catch-up growth after malaria; $40 for teachers participating in a trial of a school-based intervention. Tables 3 and 4 show the reported incentive use and types of incentives used stratified by continent of recruitment. The use of incentives was most often reported in studies that recruited from North America (n = 33/119, 28%). All studies that offered incentive payments recruited from North America.

The child was often the recipient of the incentive, rather than the parents or family: 20% (n =1/5) of reimbursements (e.g., $5 for a bus ticket for travel), 48% (n = 10/21) of compensation incentives (e.g., $10 for completing a survey), 50% (n = 6/12) of tokens of appreciation (e.g., $10 gift certificate), and 83% (n = 5/6) of incentive payments (e.g., $50 supermarket gift cards) were intended for the participant.

Table 3. Use of incentives stratified by recruitment continent (N = 300)*

Recruitment continent	N	Use of incentives, n (%)		
		Yes	No	Not reported
Africa	26	3 (11.5)	1 (3.8)	22 (84.6)
Asia	82	1 (1.2)	2 (2.4)	79 (96.3)
Australia	18	3 (16.7)	0 (0.0)	15 (83.3)
Europe	54	2 (3.7)	3 (5.6)	49 (90.7)
North America	119	33 (27.7)	0 (0.0)	86 (72.3)
South America	9	0 (0.0)	0 (0.0)	9 (100.0)

*Some studies recruited participants from more than one continent.

Table 4. Types of incentives used stratified by continent (N = 42)*

Recruitment continent	N	Types of incentives used, n (%)			
		Compensation	Tokens of appreciation	Reimbursements	Payments
Africa	3	2 (66.7)	1 (33.3)	1 (33.3)	0 (0.0)
Asia	1	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Australia	3	1 (33.3)	0 (0.0)	2 (66.7)	0 (0.0)
Europe	2	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
North America	33	16 (48.5)	10 (30.3)	2 (6.1)	7 (21.2)
South America	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*Some studies offered multiple types of incentives.

Recruitment target attainment

About half (n = 145/300, 48%) of the trials reported sufficient information to determine if the recruitment target was achieved (Table 5). Of these, 70% (n = 102/145) recruited their target sample size. Of the studies that recruited their target sample size, four (3.9%) reported using incentives and three (2.9%) explicitly reported not using incentives.

Recruitment delays were reported in 6% (n = 19/300) of trials, and were most often due to patient level (n = 10/19, 53%; e.g., travel, duration of trial, preferences) or trial level factors (n = 9/19, 47%; e.g., funding, trial management, feasibility). Strategies to address recruitment delays included stopping the trial before the recruitment target was achieved (n = 13/19, 68%), extending the recruitment period (n = 3/19, 16%), adding trial sites (n = 2/19, 11%), modifying the eligibility criteria (n = 3/19, 16%), and modifying the incentives (n = 1/19, 5%).

Table 5. Recruitment target attainment (N = 300)

Characteristic	n (%)
Sample size	
Calculation reported	155 (51.7)
Recruitment target reached*	102/145 (70.3)
Recruitment delays reported	
Yes	19 (6.3)
No	281 (93.7)
Types of recruitment delays**	
Patient level factors	10/19 (52.6)
Trial level factors	9/19 (47.4)
Site level factors	1/19 (5.3)
Trial team level factors	1/19 (5.3)
Not specified	4/19 (21.1)

How recruitment delays were addressed***	
Stopping the trial before reaching the target	13/19 (68.4)
Extending the recruitment period	3/19 (15.8)
Modifying the eligibility criteria	3/19 (15.8)
Adding additional trial sites	2/19 (10.5)
Modifying incentives	1/19 (5.3)

*Based on sample size calculation and number randomized; data for this calculation were unavailable for 10 trials that reported a sample size calculation.
**Total exceeds 19 because some trials reported more than one type of delay.
***Total exceeds 19 because some trials reported more than one method.

DISCUSSION

This study addresses some of the knowledge gaps and priorities identified by StaR Child Health's Consent and Recruitment Standard Development Group.[3] We found that details of consent and recruitment procedures were infrequently reported within publications of pediatric trials. Although most trials reported obtaining consent, elaboration on the consent and recruitment process was not common. Our previous evaluation of risk of bias and trial registration among the same sample of trials and comparison to trials published in 2007 showed that some aspects of trial reporting had improved over time (e.g., reporting of allocation concealment improved and trial registration doubled). Because the trials evaluated herein were undertaken before the publication of the StaR Child Health Standards (and prior to the development of a number of international pediatric trials initiatives to improve infrastructure and research capacity in child health),[10] it is reasonable to speculate that research published today would be more completely reported compared to what we have presented. Nevertheless, reporting shortcomings likely remain and ongoing evaluation of the state of the research will be needed to inform areas in particular need for improvement.

Despite being widely accepted as a requirement,[11, 22] there remains ambiguity about what constitutes assent in pediatric trials,[23] which children are capable of providing it,[23] and how it should be reported.[24] Recently, Tait and Geisser (2017) established an operational definition of assent, including recommendations about the level of information appropriate for different ages.[25] Nevertheless, guidance on the age at which children must provide assent varies substantially by country.[26-28] It also remains unclear whether the level of detail regarding consent and recruitment procedures required by research ethics boards is appropriate or necessary in published reports of pediatric trials. In 2010, Saint-Raymond et al. called attention to the need for reporting guidelines specific to research with children.[24] The

development of pediatric adaptations of the Standard Protocol Items: Recommendations for Interventional Trials[29] and Consolidated Standards of Reporting Trials[30] statements is underway.[31]

Fewer than 20% of trials reported who approached families to participate. Although a relationship to the person obtaining consent can encourage recruitment,[32] when the person is the child's healthcare provider parents may worry that refusing participation will impact their child's quality of care.[23] In most trials of school-aged children, trial information was directed to both parents and children. Parents' and children's understanding of trial materials are fundamental to ethical and efficient recruitment.[3] Not understanding trial information discourages parents and children from enrolling in trials,[32] and some presentations of the benefits and risks of trial participation (e.g., as dense text documents) can be difficult for parents to understand.[33] The integrated consent model in which clinicians engage the trial participant in a consent conversation similar to usual care and additionally present the opportunity for the randomization of previously validated treatment options, has been proposed.[34] This approach has been suggested for low-risk and pragmatic trials,[34] however the applicability to pediatric trials needs to be established.

Few trials reported whether incentives were used, but of those that did, many were intended for children. Trial participation can be costly for families, and there is general consensus that they should be reimbursed for the related expenses (e.g., travel, parking) at a rate that is sufficient but does not lead them to undervalue risks or coerce them to consent.[22, 32] As children value incentives differently than adults, their provision to minors is controversial.[3, 10] When incentives are used, it is critical that children understand the implications of the trial and that the incentives do not influence their decision to participate.[3, 10] As mentioned previously, allowable payment incentives for children who participate in trials vary by region. As expected, just 4% of studies that recruited in Europe reported providing incentives, all of which were in the form of compensation. Conversely, 28% of studies that recruited in North America reported providing incentives, and 21% percent of these were in the form of payments. Given the poor reporting of incentive use, it was not possible to conclude whether offering incentives improved the chance of attaining the recruitment target. Nevertheless, from the few studies that reported whether or not incentives were used, it did not appear that this was the case.

Seventy percent of trials met their recruitment targets. This is substantially greater than the 29% reported in St-Louis et al.'s review of pediatric general surgical trials,[35] and the 55% in Sully et al.'s review of multicenter trials in the United Kingdom.[36] Failing to meet the recruitment target contributes to research

waste when the trial is underpowered to detect clinically important differences.[37] Due to reporting deficiencies, we could only ascertain whether trials achieved their recruitment targets for half of the sample. Whether transparent reporting is biased toward trials that meet their recruitment targets is not yet known.

Strengths and Limitations

We have highlighted a number of conduct and/or reporting gaps in an effort to contribute to the ongoing research agenda. Our sample will serve as a baseline for ongoing monitoring of consent and recruitment procedures in pediatric trials. The extracted data were limited to those available within published reports, therefore we cannot ascertain the extent to which the findings reflect conduct and/or reporting shortcomings. Because the sample included studies that reported on participants aged 0 to 21 years and from countries that varied by income, the sample was highly heterogeneous (i.e., consent procedures are different for infants compared to adolescents and young adults, and are highly influenced by cultural norms and local ethical standards) limiting generalizability to specific age groups or regions by income level. Further investigation into trials examining participants in more discrete age groups (e.g., infants, young children, adolescents) and in regions of a specific income level (e.g., low income, middle income) would be of interest. As we used a sample of trials published in 2012, the findings may not be generalizable to other years.

CONCLUSIONS

In our sample, five reporting shortcomings were evident: how families were recruited; who obtained consent and/or assent and how; who trial information was directed to; whether incentives were used; and sufficient data to determine if the recruitment target was met. Forthcoming reporting guidance specific to pediatric trials[31] and the StaR Child Health Standards[3] may contribute to improving the conduct and reporting of pediatric trials in this priority area. Using this study as a baseline, continued monitoring of the state of the research will allow for the identification of changes over time and the need for the translation of evidence-based standards into forms that are appealing and accessible to trialists.

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COMPETING INTERESTS

We have no financial or other conflicts of interest to declare.

CONTRIBUTORS' STATEMENT

Dr Dyson conceptualized the study, designed the data collection instrument, supervised all aspects of the work, verified and analyzed the extracted data, and contributed to drafting the manuscript.
Dr Gates verified and analyzed the extracted data, contributed to drafting the manuscript, and completed revisions of the manuscript drafts following input from the other authors.
Drs Caldwell, Curtis, Dans, Hartling, Kelly, Fernandes, Woolfall, and Williams contributed to the interpretation of the extracted data, and revised manuscript drafts critically for important intellectual content.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DATA SHARING STATEMENT

The data collected and analyzed from trials included in this study will be available to researchers via reasonable request from the corresponding author. The data will be available immediately following, and for 5 years after article publication. Our data extraction guide is available as a supplementary file.

PREVIOUS PRESENTATION

Parts of this research were presented as a poster at our local research day (Pediatric Research Day, Department of Pediatrics, University of Alberta, Edmonton, Canada) on 16 May 2018 under the

following title: “The safe and ethical participation of children in research: a descriptive analysis of the conduct and reporting of trials published in 2012”.

REFERENCES

1. Wittmeier KD, Craig J, Klassen TP, et al. The mission of StaR Child Health is to improve the quality of the design, conduct, and reporting of pediatric clinical research by promoting the use of modern research standards. Introduction. *Pediatrics* 2012;129(Suppl 3):S111.
2. 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):S112-17.
3. Caldwell PH, Dans L, de Vries MC, et al. Standard 1: consent and recruitment. *Pediatrics* 2012;129(Suppl 3):S118-23.
4. Ellenberg S, Fernandes RM, Saloojee H, et al. Standard 3: data monitoring committees. *Pediatrics* 2012;129(Suppl 3):S132-7.
5. Hartling L, Hamm M, Klassen T, et al. Standard 2: containing risk of bias. *Pediatrics* 2012;129(Suppl 3):S124-31.
6. 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):S146-52.
7. van der Tweel I, Askie L, Vandermeer B, et al. Standard 4: determining adequate sample sizes. *Pediatrics* 2012;129(Suppl 3):S138-45.
8. Williams K, Thomson D, Seto I, et al. Standard 6: age groups for pediatric trials. *Pediatrics* 2012;129(Suppl 3):S153-60.
9. 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.
10. Joseph PD, Craig JC, Caldwell PH. Clinical trials in children. *Br J Clin Pharmacol* 2015;79(3):357-69.
11. Graham A, Powell M, Taylor N, et al. Ethical research involving children: putting the evidence into practice. *Family Matters* 2015;96:23-8.
12. Ioannidis JP, Greenland S, Hlatky MA, et al. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet* 2014;383:166-75.
13. Glasziou P, Altman DG, Bossuyt P, et al. Reducing waste from incomplete or unusable reports of biomedical research. *Lancet* 2014;383:267-76.
14. Nayak BK. Understanding the relevance of sample size calculation. *Indian J Ophthalmol* 2010;58:469.

15. 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.
16. Cochrane. Cochrane Central Register of Controlled Trials (CENTRAL). London, United Kingdom: Cochrane. c1999-2018. Available from: http://www.cochranelibrary.com/about/central-landing-page.html. Accessed 5 September 2018.
17. Thomson D, Hartling L, Cohen E, et al. Controlled trials in children: quantity, methodological quality and descriptive characteristics of pediatric controlled trials published 1948-2006. PLoS One 2010;5:e13106.
18. 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.
19. World Health Organization. Classifications. International Classification of Diseases (ICD). ICD-10 online versions. Geneva, Switzerland: World Health Organization. 2018. Available from: http://www.who.int/classifications/icd/icdonlineversions/en/. Accessed 5 September 2018.
20. The World Bank. World Bank Country and Lending Groups. Washington, District of Columbia: The World Bank. 2018. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. Accessed 11 September 2018.
21. Kaur G, Smyth RL, Williamson P. Developing a survey of barriers and facilitators to recruitment in randomized controlled trials. *Trials* 2012;13:218.
22. General Assembly of the World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191-4.
23. Leibson T, Koren G. Informed consent in pediatric research. *Paediatr Drugs* 2015;17:5-11.
24. Saint-Raymond A, Hill S, Martines J, et al. CONSORT 2010. *Lancet* 2010;376(9737):229-30.
25. Tait AR, Geisser ME. Development of a consensus operational definition of child assent for research. *BMC Med Ethics* 2017;18:41.
26. Shaddy RE, Denne SC, The Committee on Drugs and Committee on Pediatric Research. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Pediatrics* 2010;125:850-60. Reaffirmed January 2014; 133:e1479.
27. Lepola P, Needham A, Mendum J, et al. Informed consent for paediatric clinical trials in Europe. *Arch Dis Child*. 2016;101:1017-25.

28. Canadian Paediatric Society. Ethical issues in health research in children. *Paediatr Child Health* 2008;13:707-20.
29. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200-7.
30. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Trials* 2010;11:32.
31. Clyburne-Sherin AVP, Thurairajah P, Kapadia MZ, et al. Recommendations and evidence for reporting items in pediatric clinical trial protocols and reports: two systematic reviews. *Trials* 2015;16:417.
32. Tromp K, Zwaan CM, van de Vathorst S. Motivations of children and their parents to participate in drug research: a systematic review. *Eur J Pediatr* 2016;175:599-12.
33. Tait AR, Voepel-Lewis T, Zikmund-Fisher BJ, et al. Presenting research risks and benefits to parents: does format matter? *Anesth Analg* 2010;111:718-23.
34. Kim SY, Miller FG. Informed consent for pragmatic trials: the integrated consent model. *NEJM* 2014;370:769-72.
35. St-Louis E, Oosenbrug M, Landry T, et al. Enrollment and reporting practices in pediatric general surgical randomized clinical trials: a systematic review and observational analysis. *J Pediatr Surg* 2018;53:879-84.
36. Sully BG, Julious SA, Nicholl J. A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies. *Trials* 2013;14:166.
37. Salman RA-S, Beller E, Kagan J, Hemminki E, et al. Increasing value and reducing waste in biomedical research regulation and management. *Lancet* 2014;383:176-85.

Supplementary File 1. Search Strategy

Summary of Search

Database	Date Searched	Number Retrieved	After Duplicate Removal
Cochrane Central Register of Controlled Trials (Wiley)	November 4, 2013	2343	2296
Total		**2343**	**2296**

Database: Cochrane Central Register of Controlled Trials (Wiley)

Date Searched: 4 November 2013 at 21:07:57.057

Results: 2343 records (2296 following duplicate removal)

Search Strategy:

#1 (Infant* or infancy or Newborn* or Baby* or Babies or Neonat* or Preterm* or Prematur* or Postmatur* or Child* or Schoolchild* or School age* or Preschool* or Kid or kids or Toddler* or Teen* or Boy* or Girl* or Minors* or Pubert* or Pubescen* or Prepubescen* or Pediatric* or Paediatric* or Peadiatric* or Nursery school* or Kindergar* or Primary school* or Secondary school* or Elementary school* or High school* or Highschool*):ti,ab,kw

#2 (Adolesc*):ti,ab

#3 (Infant or Child or Minors or Puberty or Pediatrics or Schools):kw

#4 #1 or #2 or #3

#5 adolescent*:kw

#6 (adolescent* and (adult* or elderly or "middle aged" or "aged, 80 and over")):kw

#7 #6 and not #4

#8 #4 or #5

#9 #8 and not #7 from 2012 to 2012, in Trials

Supplementary File 2. Data Extraction Guide

Field	Response	Comments
Trial conduct		
Where were participants recruited from?	□Low income country □Lower middle income country □Upper middle income country □High income country	Select all that apply. Classified according to the World Bank income classifications, 2019 fiscal year. Expressed as GNI per capita: **Low income country:** <$995/year **Lower middle income country:** $996 to $3895/year **Upper middle income country:** $3896 to $$12055/year **High income country:** ≥$12056/year https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups
What recruitment strategies were used?	□Standard □Not standard	**Standard:** Participants provide consent and then are randomized in a typical 1:1, 1:2, etc. manner. **Not standard:** Any of: – Open trial design (randomization occurs before participants are approached, so that participants are informed of the treatment they were randomized to receive prior to consent) – Increasing or decreasing the chance of receiving the experimental treatment – Experimental treatment for all participants and standard treatment for non-participants – Standard care for all participants and experimental treatment for non-participants – Random assignment of treatment for participants and choice of treatment for non-participants – Opt in or opt out recruitment (consent was sought for participation or non-participation)
Who first approached the patient about participating in the trial?	□Child's clinician □Researcher/clinician unknown to patient □Other (specify): □Not reported	Other professionals could include individuals such as teachers.
How did the family first	□Approached during healthcare	Select all that apply.

Supplementary File 2. Data Extraction Guide

hear about the trial?	visit □Generalized mailing □Targeted mailing □Personalized mailing □Phone calls □Media □Pamphlets □Not reported □Other (specify):	**Generalized mailing:** mail out to a large population **Targeted mailing:** mail out to a targeted group **Personalized mailing:** mailing addressed to the individual **Media:** Internet, newspaper, radio, TV **Pamphlets:** given to the families or left out for participants to pick up
Who was the trial information targeted to?	□Parents □Children □Both □Not reported	"Trial information" refers to recruitment materials.
Did the authors report that consent was obtained?	□Yes □No	
If yes, who obtained consent from the participants?	□Child's clinician □Researcher/clinician unknown to patient □Other (specify): □Not reported	Other professionals could include individuals such as teachers.
If yes, how was consent provided in the study?	□Parental permission □Parental permission and participant assent □Consent of a mature minor □N/A	Can assume parental consent if consent reported but not specified, and no other indication that another model was used.
Were any incentives used in the study?	□Yes □No □Not reported	
If yes, what incentives were used?	□Reimbursement □Parents □Child □Families (no other detail) □Not reported □Compensation □Parents	Select all that apply. **Reimbursement:** costs associated with participation in the study (e.g., travel, parking) are paid back. **Compensation:** participants are paid a modest amount for their time/effort. **Appreciation:** a small token gift given at the end of the study, usually not known beforehand.

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	□Child □Families (no other detail) □Not reported □Appreciation □Parents □Child □Families (no other detail) □Not reported □Payment □Parents □Child □Families (no other detail) □Not reported □N/A	**Payment:** typically known before study participation and used as a strategy to enhance recruitment. *Use "families" only if specified as such in the publication, with no information provided on whether the incentives were meant for the parents or child.
How long were participants given to decide whether or not to enroll in the trial?	□No restriction □Limited □No time □Not reported	**No restriction:** hours to weeks **Limited:** immediately to less than a few hours **No time:** retrospective consent
Were any delays, shortfalls, or difficulties in recruitment reported once the trial was underway?	□Yes □No	
If yes, what were the reasons for the delays or difficulties?	□Trial level factors □Site level factors □Patient level factors □Clinical team level factors □Information and consent factors □Study team level factors □Other (specify): □N/A	Examples (for more detail, see *Kaur Trials 2012*): **Trial level:** funding, trial management, feasibility **Site level:** competing projects, time to open up site **Patient level:** travel, costs, duration of trial and follow-up, preferences, language or cultural barrier **Information and consent:** amount and complexity of trial information provided, experience of clinical team seeking consent **Study team level:** experience and training of team, clinical workload, clinician attitude towards research or treatment
How were the recruitment delays or difficulties addressed?	□Described (specify): □Not described □No difficulties	
Was the use of patient or	□Yes (specify):	For involvement in the **conduct** of the study, consider involvement past the

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family involvement in the design or conduct of the study reported?	□No	point where a decision is made to participate, i.e., the participant/family has already enrolled prior to the involvement referred to.
How was the study population selected?	□Inpatients □NICU □PICU □Not reported □Other (specify): □Outpatients □Clinicians' office □School □Community □Unclear □Other (specify):	Select all that apply. In the case of selection from a dental clinic, report "Doctor's office."
What primary diagnostic category was involved in the study?	□Infectious and parasitic diseases □Neoplasms □Blood, blood forming organs, and immune mechanism □Endocrine, nutritional, and metabolic diseases □Mental and behavioural disorders □Nervous system □Eye and adnexa □Ear and mastoid process □Circulatory system □Respiratory system □Digestive system □Skin and subcutaneous tissue □Musculoskeletal system and connective tissue □Genitourinary system □Pregnancy, childbirth, and the puerperium □Conditions originating in the	Select the primary diagnostic category of the study using the ICD-10 classification system. *(ICD-10 Version:2010 http://apps.who.int/classifications/icd10/browse/2010/en)*

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	perinatal period □Congenital malformations, deformations, and chromosomal abnormalities □Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified □Injury, poisoning, and consequences of external causes □External causes of morbidity and mortality □Factors influencing health status and contact with health services □Oral health □Other (specify):	
Did the study exclude participants who had at least one chronic condition (other than the condition that was the focus of the trial) or a co-morbid condition?	□Yes □No □Unclear	
Sample size		
How many patients were approached to participate in the study?		Use NR if applicable.
How many patients consented to participate in the study?		Use NR if applicable. *This is not necessarily the same number as randomized.
How many participants were randomized?		Total study n.
How many participants were analyzed?		Total study n. If the numbers differ for different outcomes or time points, report the number of participants analyzed for the primary outcome. If not specified,

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		use the **time of the first measurement**.
Was a sample size calculation reported?	□Yes □ No	
If yes, what was the calculated sample size?		