Consent Rates Reported in Published Pediatric Randomized Controlled Trials

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Objective To determine the average reported consent rate for published pediatric randomized controlled trials (RCTs) and whether this rate varies by trial characteristics.

Study design A review of pediatric RCTs published in Medline in 2009, 2010, or 2015 was performed. Secondary analyses of prior trials, trials including adults, trials not requiring consent, or trials with missing or unclear consent data were excluded. Consent rate was defined as the number of patients enrolled divided by number of eligible patients where families were approached. Random effects meta-regression was conducted to determine the weighted average consent rate.

Results Of 2347 trials identified, 1651 were excluded. An additional 418 of 696 (60%) were excluded because the consent rate was missing or unclear. The average consent rate for 278 included RCTs was 82.6% (95% CI, 80.3%-84.8%) and was higher for vaccination compared with behavioral trials and for industry-funded compared with National Institutes of Health-funded or other government-funded trials. The average consent rate was <70% for 26% of included trials. Of these trials, US trials (28/77 [36.4%]) had a higher probability of a consent rate of <70% than non-US studies (35/64 [21.3%]) and multinational (9/37 [24.3%]) studies. There was slight variation by funding category.

Conclusions Although the average consent rate for published trials was reasonably high, approximately one-quarter of trials had consent rates of <70%. Consent rates reporting has improved over time, but remains suboptimal. Our findings should assist with the planning of future pediatric RCTs, although consent data from unpublished trials are also needed. *(J Pediatr 2020;227:281-7)*.

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Randomized controlled trials (RCTs) are the gold standard for clinical research, but are challenging to conduct, especially in children. Discontinuation and nonpublication of trials limit the advancement of evidence-based medicine.[1,2] Described barriers to trial execution and completion include difficulties with recruitment which may stem from unique challenges specific to informed consent in pediatrics including the requirement that parents consent on behalf of their children.[3-5] Prior research has suggested areas for improving the process of informed consent in pediatrics, but data are scarce surrounding consent rates and whether RCT characteristics impact consent.[4,6,7] Predicting recruitment is important when planning an RCT, creating a budget, and determining feasibility. We aim to identify the average consent rate in published pediatric RCTs. Our secondary aim was to identify the influence of trial size, intervention type, control and setting of the studies (inpatient, outpatient, etc) on the consent rate.

Methods

The search strategy identified RCTs published and catalogued in Medline. The PubMed search strategy was generated using standard filters and Medical Subject Headings (MeSH). The search strategy: "((Randomized Controlled Trial[ptyp] AND ("2009/01/01"[PDat]: "2009/12/31"[PDat]) AND Humans[MeSH] AND English[lang] AND jsubsetaim[text] AND (infant [MeSH] OR child[MeSH] OR adolescent[MeSH]))" was limited to human participants, infants and children (0-18 years of age). Dates were adjusted and the search strategy rerun for 2010 and 2015. In 2011-2012, we reviewed RCTs from 2009 and 2010 but did not publish these results. We updated this review in 2017-2018 with data from RCTs published in 2015 to evaluate for any temporal trends.

CONSORT	Consolidated Standards of Reporting Trials
MESH	Medical subject headings
NIH	National Institutes of Health
RCT	Randomized controlled trial

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Identification and Data Extraction

Two authors independently performed each aspect of trial identification, review and data extraction. Trials were independently reviewed. Trial identification began with a search of Medline via PubMed using the standard filters and search strategy described elsewhere in this article, followed by an examination of titles and abstracts. Trials were excluded if they had a year of print publication that was not 2009, 2010, or 2015; were duplicate reports; were not RCTs; did not require informed consent; included adults as trial participants; represented a secondary analysis of a prior published RCT; or the consent rate was missing or unclear (Figure 1). Duplicate reports were those for which the same trial had different publication dates, that is, print and e-publication dates in differing years. For the purpose of standardization, the year of print publication was considered final. Once an exclusion criterion was apparent, that criterion was selected as the reason for exclusion such that each excluded article was coded as having only 1 exclusion criterion. Secondary analyses were excluded to prevent double counting. A trial was considered to involve adult participants if any participants were >18 years of age or if it involved a parent-child dyad (eg, a vitamin supplement was given to a breastfeeding mother and outcomes were measured on the child). The "consent rate missing or unclear" criterion was the final exclusion criterion to be considered and was intended to answer the question "what proportion of pediatric RCTs report a consent rate?" As an example illustrating "unclear" consent rates, some trials reported that "consent was obtained for all patients included in the study," but did not quantify refusals or total number of families approached. Disagreements were resolved by consensus after re-review. No formal appraisal of trial quality was undertaken because we were not attempting to analyze trial results and implications of findings.

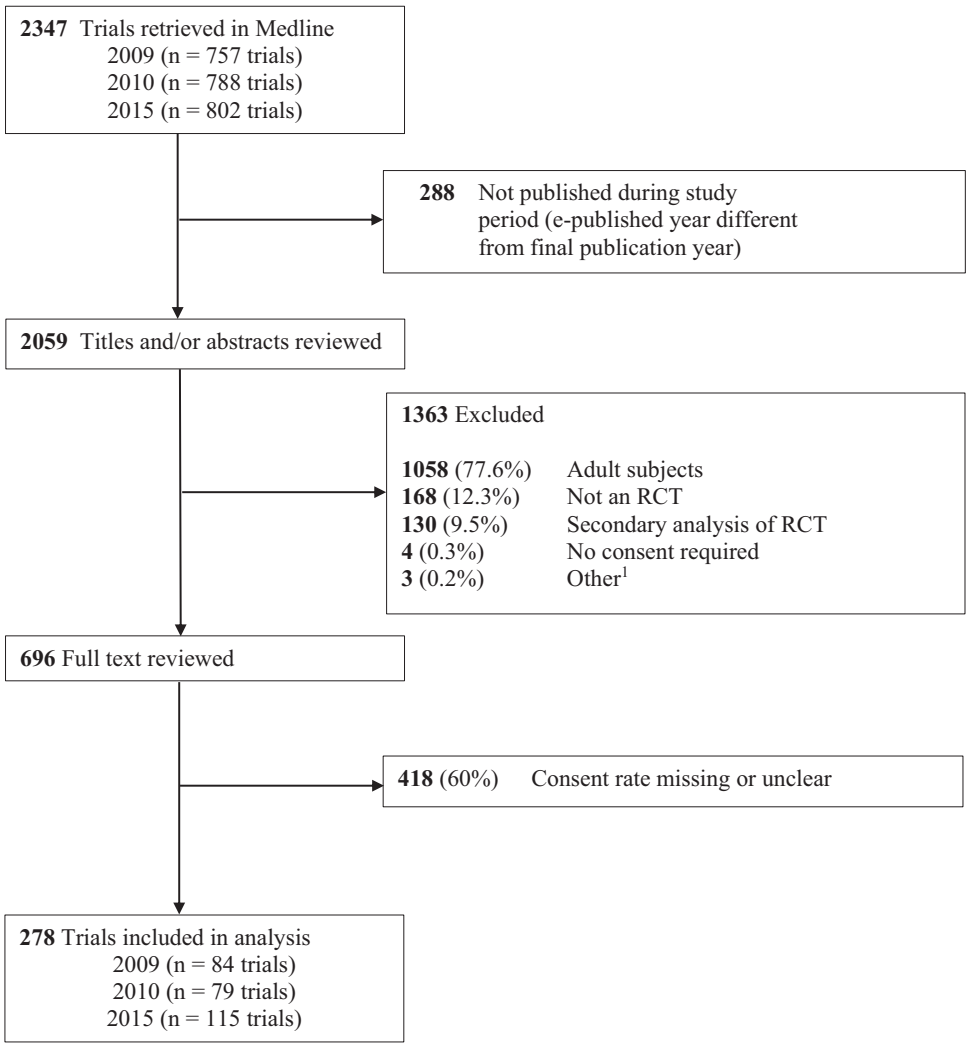

Figure 1. Flow diagram of studies from database identification via PubMed search strategy to inclusion in data analysis. [1]Other: 3 trials were excluded for reasons not otherwise indicated: animal subjects, recruitment advertised, and recruited from another RCT.

Definitions and Data Characterization

We use the term "consent rate" to describe a proportion, in keeping with the common nomenclature used by other studies on informed consent.[8,9] The proportion was calculated by dividing the total number of children whose parents provided consent by the sum of eligible children whose parents were approached and invited to participate. Our overarching intent was to characterize how often parents of eligible children agree to participate, and thus assent was not part of this study. Twins/siblings were considered as separate participants given the possibility that parents may agree to enroll one child but not another.

Trial characteristics are indicated in Figure 2. We defined the country of each RCT as US, non-US, or multinational. If an RCT included the US and another nation, it was labeled multinational. The intent in exploring the RCT country of origin was to assess whether cultural or administrative factors might impact consent rates. The setting was labeled where recruitment occurred, with emergency department studies characterized as outpatient. We assessed if compensation was provided to participants for involvement in the trial. Compensation was categorized as given or not given/not specified. We did not delineate who (parent, patient, or both) received compensation or the type of compensation received.

Statistical Analyses

We used a κ statistic to report interobserver agreement for trial inclusion. To conduct random-effects meta-analysis, we first stabilized the variances of the raw consent rates using a Freeman-Tukey double arcsine transformation and avoided the generalized linear mixed model because it can have problems with convergence and does not generate a weighting estimate to reflect the contribution of individual studies (or types of studies) on the overall estimate.[10] We then modeled the heterogeneity of these transformed consent rates using the Knapp-Hartung method, which makes small sample adjustments to variances and constructs CIs and *P* values based on a *t*-distribution.[11] We generated separate meta-regression models for each of 8 subgroup analyses: type of intervention, type of control, setting, country, funding, premature termination, participant compensation, and publication year.[12] Subgroups were entered as 'dummy coded' indicator variables into these models to derive the *P* values for comparisons between each subgroup and its referent, as well as the back-transformed average consent proportions and CIs for each subgroup.[13] A χ^2 test was conducted to compare the percentage of published pediatric RCTs for which the consent rate was missing or unclear for 2009-2010 and 2015. Post hoc analyses with χ^2 tests were conducted to compare characteristics for trials with consent rates of <70%.

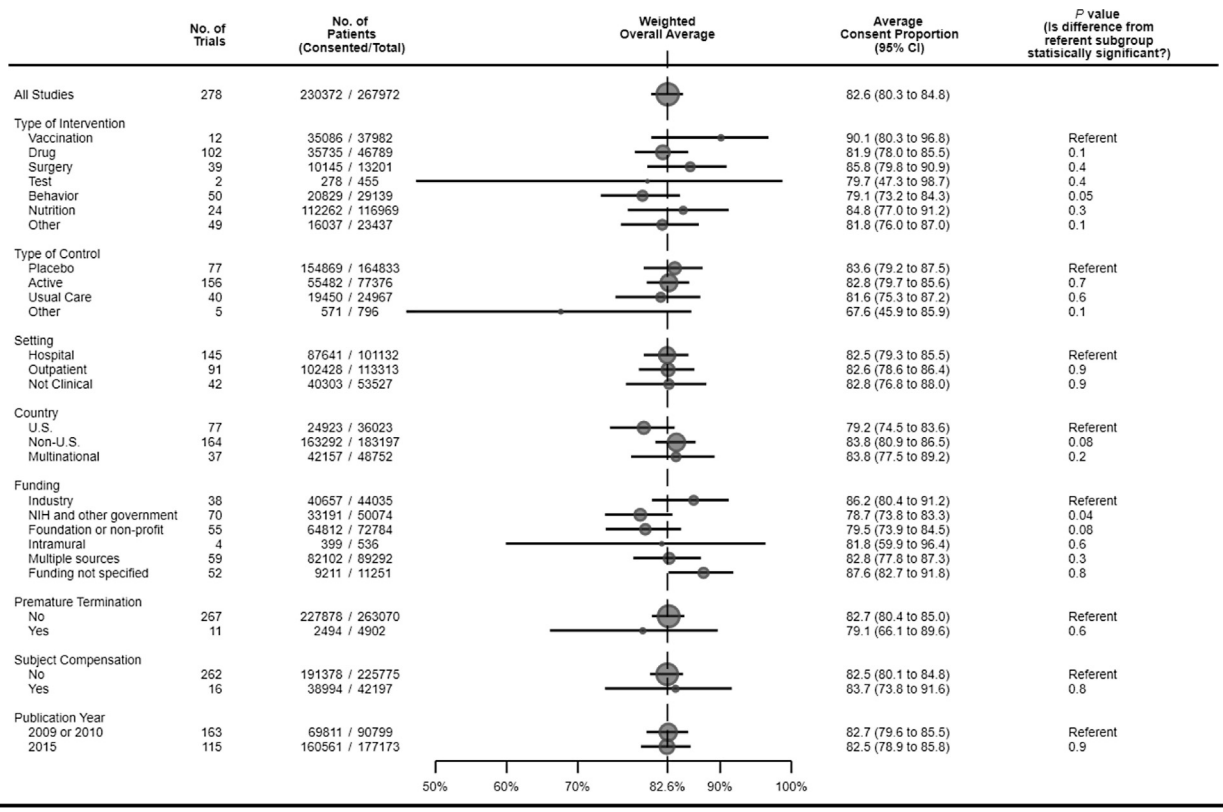

Figure 2. Average consent proportion analysis by RCT characteristics. Dashed vertical line represents weighted consent rate for all studies.

Results

We identified 2347 published pediatric RCTs using our search strategy and removed 288 studies for having an inaccurate year of publication (2011 or 2016) or being duplicate reports. Two reviewers manually reviewed 2059 titles and abstracts and excluded 1363 trials. The remaining 696 trials were reviewed in full text. The consent rate was missing or unclear in 418 of 696 trials (60%), leaving 278 for analysis (Figure 1). The kappa for trial inclusion was 0.802. Three trials were excluded during trial and abstract review for the following reasons: animal participants, recruitment advertised, and recruited from another RCT. We excluded the trial where recruitment was advertised given that the consent process would involve a preselected group that would likely be more interested in participating in the trial. The proportion of trials with a missing or unclear consent rate decreased over time from 64.5% in 2009-2010 to 50.9% in 2015 ($P = .001$). We conducted a post hoc analysis of 20 randomly selected trials from those excluded for the criterion missing or unclear consent rate. We reviewed available data for these trials on clinicaltrials.gov and no additional consent rate information was identified.

Trial Characteristics

Of the included trials, 77 of 278 (28%) were conducted in the US, 164 of 278 (59%) were conducted in one country outside the US, and 37 of 278 (13%) were multinational. The most common type of intervention involved a drug or medication (102/278 [37%]). A majority of trial controls were other interventions 156 of 278 (56%), followed by placebo controls 77 of 278 (28%), then usual or standard care 40 of 278 (14%). A majority of RCTs (145/278 [52%]), were conducted in the inpatient setting. A funding source was not specified in 52 of 278 (19%) of published RCTs. The most common funding source for published pediatric RCTs was the National Institutes of Health (NIH)/government, but this only accounted for 70 of 278 (25%), with the second most likely form of funding being multiple sources 59 of 278 (21%). Only 11 of the 278 (4%) included trials documented premature termination.

Consent Rates

The weighted average consent rate for the 278 trials was 82.6% (95% CI, 80.3%-84.8%). We noted slight variability in the consent rate by trial characteristics (Figure 2). The consent rate was highest for vaccine trials 90.1% (95% CI, 80.4%-96.8%) and lowest for behavioral interventions 79.1% (95% CI, 73.2%-84.3%; $P = .05$). Consent rates were higher in trials with industry funding compared with NIH or other government funding: 86.2% (95% CI, 80.4%-91.2%) and 78.7% (95% CI, 73.8%-83.3%), respectively ($P = .04$). Consent rates for non-US studies compared with US studies were 83.8% (95% CI, 80.9%-86.5%) and 79.2% (95% CI, 74.5%-83.6%), respectively, but this difference was not statistically significant ($P = .08$). No other trial characteristics achieved statistical significance. Consent rates were <70% for 26% of trials and <60% for 19% of trials (Figure 3). A post hoc analysis of trials with consent rates of <70% showed 2 statistically significant associations:

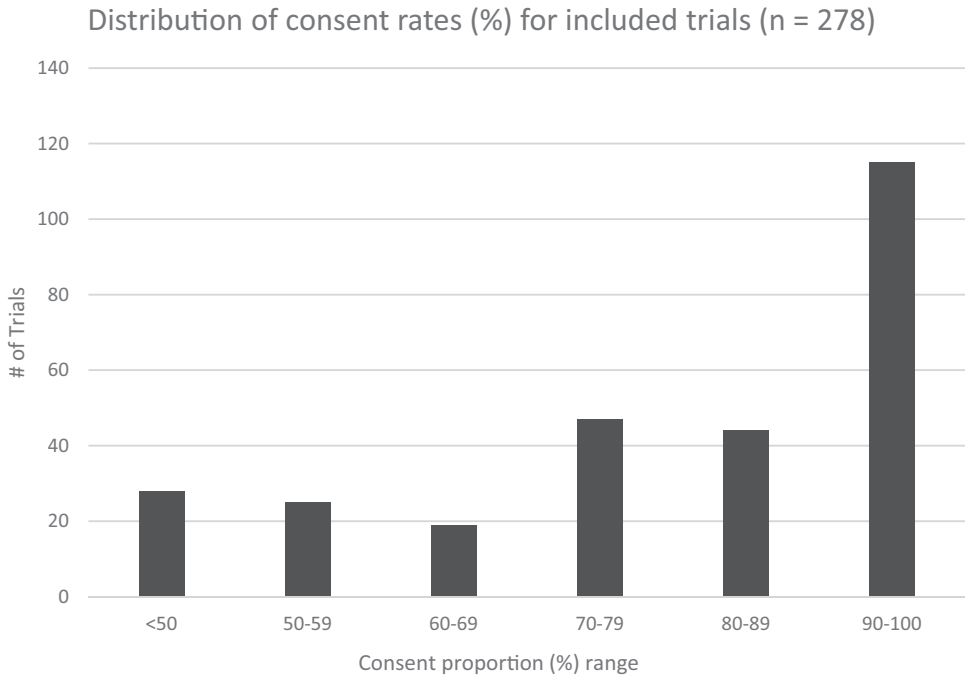

Figure 3. Distribution of consent rates for included trials.

country of origin ($P = .05$) and funding ($P = .04$). US studies (28/77 [36.4%]) had a higher probability of a consent rate of <70% than non-US (35/164 [21.3%]) and multinational (9/37 [24.3%]) studies. There was slight variation in probability of consent rate <70% by funding category: local/intramural (2/4 [50%]), foundation/nonprofits (18/55 [32.7%]), industry funding (11/38 [29%]), NIH/government (20/70 [28.6%]), multiple (16/59 [27.2%]), or not specified (5/52 [9.6%]).

Discussion

In this review of pediatric RCTs published in 2009, 2010, or 2015, the average weighted consent rate was 82.6% (95% CI, 80.3%-84.8%) and one-quarter of trials had a consent rate of <70%. We found statistically significant differences within subgroups for type of intervention and funding source. Despite a modest improvement in the percentage of published trials that provide consent rate information between 2009-2010 and 2015, transparency around reporting consent rates remains suboptimal. This lack of quantification of trial participation limits the generalizability of trial findings. Our results should be interpreted with caution given that we only investigated consent rates reported in published trials. Among all initiated pediatric RCTs, including those that terminated early owing to poor enrollment, consent rates are likely lower.

The average consent rate was higher than we anticipated, but is still slightly lower than that of an adult critical care study, which found a median consent rate of 86.9%, confirming prior studies indicating the added challenge of consent in pediatric trials.[8] To our knowledge, there are no other publications that explore the average reported consent rate in pediatric RCTs. Research continues to study how we can improve consent rates in randomized trials, including a recent Cochrane review investigating strategies for improving recruitment of participants (pediatric and adult).[14] In pediatrics, ongoing efforts exist trying to develop interventions that will boost recruitment in randomized trials.[15] There is a growing body of evidence to identify factors inherent to participants and the consent process that influence success.[9,16-27] One study indicated preference for who approaches, introduces, and obtains consent from the patient/parent. Some parents prefer to be approached by the physician caring for the child, or the pediatrician with whom they have a long-standing relationship.[27,28] Many parents dislike the concept of randomization.[24] Some parents feel there is suboptimal transfer of specifics regarding the consent process and trial details.[28] From the provider perspective, some providers fear that the introduction of research may place undue burden on parents.[23,24] This juxtaposition of provider and parent perspectives highlights the complicated nature of informed consent in pediatrics and requires additional research to elucidate methods to circumvent both provider and parental concerns.

In addition to the consent process, we sought to assess whether characteristics inherent to the trial influenced consent rates. We found statistically significant differences within subgroups for the type of intervention and funding source, where vaccination trials had a higher consent rate than behavioral trials. Given that some vaccination trials occur in developing countries, these trials may represent the only access to immunization, which in turn could lead to higher consent rates. Consent rates were higher for trials funded by industry compared with trials funded by the NIH or another government source. Possible explanations for the difference between industry-funded and NIH-funded trials might include different populations studied, incentives for participation, and resources to assist with consent. Funding may play a role in various aspects of trial success including consent rates, the likelihood of trial completion, and ultimate publication of results.[1,2,29]

We explored whether US trials were more likely to have lower consent rates than trials conducted outside the US, perhaps owing to cultural factors and/or different guidelines. The widespread attention to issues surrounding informed consent in the SUPPORT trial may have also had an impact on families' views on participation. We do know that there are differences in the consent process in different countries, which likely contributes to consent rate. A recent publication expands upon differences in obtaining informed consent in other countries, urging greater adoption of a formalized and informative consent process based on various international guidelines.[30,31]

Our findings demonstrate a lack of transparency in reporting consent rates in pediatric RCTs. The consent rate was missing or unclear in more than one-half (60%) of the RCTs reviewed. This is similar to the review of adult critical care studies where consent rate was not reported in 69.2% of published trials.[8] Multiple studies included a generic statement indicating that consent was obtained in all participants, but did not indicate numbers for refusal. This lack of transparency challenges the validity and generalizability of trial results, creating what some deem a "crisis of credibility" that can be viewed as a threat to pediatric research.[32]

Fortunately, consent rate reporting in pediatrics has improved over time, likely in part owing to the Consolidated Standards of Reporting Trials (CONSORT) statement. Initially published in 1996 and revised in 2001 and 2010, the CONSORT statement provides guidelines for reporting the methodology and findings of RCTs.[33] Between 2009-2010 and 2015, the percentage of trials that reported consent rate data increased from 35% to 49%. This improvement may stem from wider dissemination and implementation of the CONSORT guidelines (www.consort-statement.org) that were updated in 2010. Nonetheless, more than one-half of the 2015 trials did not report consent rates, although this proportion may be lower now as journals increasingly require adherence to the CONSORT guidelines. Specifics regarding consent rate are not required within CONSORT and others have postulated such items be added to the CONSORT checklist to improve the standardization of pediatric trials,

including child-specific ethics approval based on Good Clinical Practice.[34] One could argue additional data on consent rate reporting could improve the planning and standardization of pediatric trials. This review demonstrates that improved transparency surrounding consent and trial characteristics is needed and can enhance the development, budgeting, feasibility, and implementation of future trials.

This study was limited by a lack of information on unpublished trials. Although clinicaltrials.gov has greatly enhanced the transparency surrounding the planning and execution of RCTs, data on consent rates for unfinished trials are not available. Unpublished RCTs, especially those that were never completed because of recruitment challenges, may have had lower consent rates and future work should quantify consent rates in unpublished studies. Similarly, the fact that a majority of trials do not report consent rates impacts the generalizability of our findings. We did not communicate with the authors of excluded trials, including the 60% of trials for which there were missing consent data, but our review of randomly selected trials was unsuccessful in identifying any additional data on consent rates on clinicaltrials.gov. The presented data are now 5-11 years old but, given the consistency in consent rates between publication years, these findings should still be applicable today. There may be additional characteristics of RCTs that could influence consent, such as trial phase, but specific language was not consistently included in the reviewed trials. Assent is an important construct related to parental consent. We were unable to quantify assent rates in this study because a majority of trials did not report assent vs consent rates. Further research should examine the impact of assent on overall consent. We were not able to determine the details of the consent process for each study, so there may have been additional unmeasured aspects of consent that impacted success rates. Last, it is possible that not all refusals are documented and recorded, and that families who are perceived as being unlikely to consent may not be approached in the first place.

The average consent rate reported in published pediatric RCTs was 82.6% (95% CI, 80.3%-84.8%) with minor variability by trial characteristic. Approximately one-quarter of RCTs have consent rates of <70%, and this threat to generalizability of findings from trials with low consent rates constrains our ability to strengthen the evidence base in pediatrics. Improved transparency surrounding consent can enhance the development, budgeting, feasibility, and implementation of future trials. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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