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Trial Characteristics That Affect Parental Consent in Neonatal Drug Trials

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Abstract

Objective—The main purpose of this article is to determine parental consent rates in neonatal drug trials and describe trial characteristics associated with higher rates.

Study Design—We included neonatal drug trials published between 2009 and 2014 and compared parental consent rates among the following characteristics: phase type, gestational age, randomization type, drug administration route, drug dosing frequency, blood sampling, control type, length of study, funding source, and length of treatment. We compared characteristics using chi-square, Fisher's exact, one-way analysis of variance or Kruskal–Wallis tests.

Results—We identified 52 trials: 38 trials (73%) reported data of parental consent. Median percentage (interquartile range) of parental consent was 79% (62, 89). Higher rates were observed in studies that used active comparators (87%) and shorter study lengths (81% for studies <24 hours).

Conclusion—Parental consent rates for neonatal drug trials varied by study characteristics. Information on proportion of parents consented is valuable to assess generalizability of trial results and for preparing trial protocols.

Keywords

newborn; clinical trial; parental consent; informed consent

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Authors' Contributions

I.B.H. and S.A. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: M. M.L., I.B.H., M.B., S.A., D.T. Acquisition, analysis, or interpretation of data: I.B.H., S.A., M.B., D.T. Drafting of the manuscript: I.B.H. Critical revision of the manuscript for important intellectual content: M.B., M.M.L., S.A., P.B.S., D.T. Statistical analysis: I.B.H. Administrative, technical, or material support: M.B., M.M.L. Study supervision: M.B., M.M.L., P.B.S.

Conflict of Interest

None.

The practice of evidence-based medicine relies on clinical trials to establish the efficacy and safety of drugs. To determine the effectiveness of interventions and the generalizability of results, a large number and wide range of patients must participate in clinical trials. Participation in neonatal clinical trials depends on informed, voluntary parental consent, and consent rates in neonatal clinical research can be low, from 48 to 71%.^{1–3} Therefore, understanding factors that affect the percentage of parental consent is an important step toward improving study participation and the validity of future neonatal research.

Parents, or other surrogates, provide consent for patients in pediatric trials. Several parental characteristics determine whether a parent is likely to consent to a trial. Positive motivators include obtaining access to new drugs and accessing a perceived superior treatment plan,^{4–6} and negative motivators include high perceived risk and antiexperimentation views.^{6,7} Decision makers might not fully understand trial characteristics; however, some study characteristics like randomization procedures and the use of placebos might negatively affect consent in clinical trials.^{8–11} Study characteristics' effects on consent rates in neonatal clinical trials have not been reported.

The purpose of this systematic review is to review clinical drug trials in infants and determine the median percentage of parental consent and identify the trial characteristics associated with higher parental consent. We hypothesize that parents are more likely to consent to phase III or phase IV clinical drug trials than phase I or phase II clinical drug trials because they presumably carry less risk with increasingly more chance for clinical benefit compared with phase I and phase II studies. Identifying differences in parental consent rates between types of clinical trials could focus efforts to optimize recruitment rate and sample size in neonatal clinical drug trials.

Materials and Methods

We followed the “Preferred reporting items for systematic reviews and meta-analyses” statement for reporting this systematic review.¹²

Search Strategy

We conducted a search of MEDLINE and EMBASE to identify neonatal clinical drug trials published between June 7, 2009 and June 5, 2014. We used the following MEDLINE MeSH terms: *therapeutic uses, physiological effects of drugs, vaccines, hormones, drug therapy, single-blind method, double-blind method, and random allocation*. We included search terms for clinical trials: *controlled clinical trial* OR randomized *controlled clinical trial*; and phase type: *clinical trial, phase I* OR *clinical trial, phase II* OR *clinical trial, phase III* OR *clinical trial, phase IV*. We also included search terms for age: *infant, newborn, neonate, and babies*. We filtered the search to include only human studies published in English. We repeated our search in EMBASE with equivalent MeSH terms. The search was conducted on June 5, 2014.

Study Selection

The search was conducted by a primary reviewer (I.B.H.). Articles that did not clearly meet the inclusion criteria during the title screen were reviewed by a team of three reviewers

(I.B. H, S.A., M.B.) to be evaluated for abstract review. We included clinical trials that evaluated drug interventions for safety, tolerability, dosing, or efficacy in neonates (birth to 28 days). We screened titles and abstracts and excluded studies that were duplicates or evaluated medical devices, procedures, food supplements, pain, or interventions for the mother. We also excluded secondary trials and trials conducted outside of the United States, Western Europe, Canada, or Australia. The initial screen was followed by a full-text review of articles.

Trial Characteristics

We extracted data from the studies using a standardized electronic form. Our review focused on the following characteristics of neonatal clinical drug trials: phase type, targeted gestational age, use of randomization, drug administration route, drug dosing (single or multiple), blood sampling, control type, funding source, maximum length of treatment, and maximum length of study period (including treatment and follow-up). After full-text review, we classified each clinical trial as a phase I, II, III, or IV study. We used the following hierarchy for classification:

1. We assigned each trial to the phase type specified in the study's full-text article.
2. If the full-text article did not list a phase type, we assigned each trial to the phase type recorded in the trial's clinicaltrials.gov registry.
3. We searched other professional trial registries (European Clinical Trials Database), International Standard Registered Clinical/Social Study Number registry, Australia New Zealand Clinical Trials Registry, and Netherlands Trial Register) to obtain phase type information not included in full-text articles or the clinicaltrials.gov registry.
4. Remaining trials were assigned a phase type through consensus by the research team. We classified phase I studies as those which evaluated drug dosing or tolerability. We classified phase II studies as those which tested a drug for safety, and we classified phase III studies as those in which the efficacy of the drug intervention was measured. A clinical trial was identified as a phase IV study if the trial measured the safety or efficacy of the drug after it was marketed.

We calculated parental consent rates for each study by dividing the number of parents who consented to the study by the number of parents approached for study participation. Authors were contacted if the published studies did not report this information. We recorded secondary trial characteristics including control type, gestational age, funding source, randomization, drug administration route, and drug dosing to determine the effect of these characteristics on parental consent rates. We extracted this information from each clinical trial and contacted authors if the published studies did not report this information.

Data Analysis

We combined phase III and phase IV studies for analysis, as both phase types represent randomized, controlled studies. We then compared the median percentage of parental consent between phase I, phase II, and phase III/phase IV studies. We also compared the median percentage of parental consent for secondary trial characteristics. In addition,

we performed a subgroup analysis evaluating differences in parental consent rates by trial characteristics among phase III and phase IV trials only. We used chi-square or Fisher's exact tests for analysis of categorical data and one-way analysis of variance or Kruskal-Wallis tests for analysis of continuous data (STATA version 12.1, College Station, TX).

Results

Our search identified 3,168 publications. After title, abstract, and full text screen, we included 51 articles in our final review, including 4 phase I studies, 15 phase II studies, 29 phase III studies, and 4 phase IV studies (►Fig. 1). One article reported two trials; therefore, a total of 52 studies were included in the final analyses. A total of 10,045 infants were enrolled in the trials; sample sizes for each trial ranged from 5 to 1384 infants. ►Table 1 summarizes the study characteristics of the included trials.

Of the 52 trials that met criteria, 38 trials (73%) reported sufficient information to determine the parental consent rates, 9 trials had incomplete data, and 5 trials did not report parental consent rates. Trials that had incomplete data or trials that did not report consent rates did not differ from trials that reported parental consent rates. Of the trials from which we could not calculate the consent rates, 57% are phase III studies, 86% are randomized, and 29% received private funding.

Median percentage of parental consent (interquartile range [IQR]) for all trials was 79% (62, 89). There was no difference in median parental consent among phase type (92% for phase I, 72% for phase II, 79% for phase III, $p = 0.36$, ►Table 2). There were differences in median parental consent among control type (72% placebo vs 87% active comparator, $p < 0.05$) and maximum length of study period (100% for <24 hours, 84% for 1–7 days, 93% for 8 days–1 month, 70% for >1 month–6 months, 53% for >6 months, and 82% for unknown study length, $p < 0.05$, ►Table 2). We observed no differences in regard to gestational age, use of randomization, drug administration route, drug dosing, blood sampling, funding source, or maximum length of treatment (►Table 2).

In a subgroup analysis, we evaluated phase III to IV trials. The median percentage (IQR) of parental consent for phase III trials was 79% (60, 87). Among phase III trials, study characteristics associated with higher parental consent rates included studies with at least one blood sample collected (83% vs 62%, $p < 0.05$), studies with active comparators (72% placebo vs 87% active comparator, $p < 0.05$), and studies with short study lengths (99% for 8 days–1 month, 80% for >1 month–6 months, 50% for >6 months, and 81% for unknown study length, $p < 0.05$, ►Table 2). There were no differences in median parental consent among targeted gestational age, drug administration route, drug dosing, funding source, or maximum length of treatment (►Table 2).

Discussion

The success of neonatal clinical trials depends on participation from a wide range of patients to discern differences between interventions and determine if the results are generalizable to other patient populations. Despite parental consent being a requisite feature of enrollment in neonatal trials, only 38 trials (73%) reported sufficient information in the publication to

calculate parental consent rates. The median percentage of parental consent for all trials was 79%, higher than previously reported estimates of 48 to 71%.^{9–11} Study phase was not associated with parental consent. However, active comparators and shorter length of study period were associated with higher parental consent. Previous research on parental consent has focused on parental characteristics, such as parental education level and socioeconomic status. We are the first to report trial characteristics in relationship to consent.^{13–16}

Our study revealed many important differences than the published literature. We found no difference in parental consent rates between phase I trials, which typically expose infants to more than minimal risk and offer little clinical benefit, and phase II, phase III, or phase IV trials, which typically carry less risk and increasingly more chance for medical benefit. This finding contrasts previous reports stating the degree of parental consent inversely varies with perceived risk.⁷ We hypothesize that parents might consent to phase I or II trials to gain access to new drugs, gain opportunities to understand their child's illness, or acquire access to perceived superior treatment options.⁵

Less than two-thirds of trials (58%) reported sufficient information in the original publication to calculate parental consent rates. The Consolidated Standards of Reporting Trials (CONSORT) does not formally require authors to report consent rates.¹⁷ The CONSORT statement does encourage authors to report how many people declined to consent to the trial, but these data are insufficient for calculating the percentage of subjects approached who consented. These data are important pieces in interpreting a trial's validity. For example, low percentages of parental consent may indicate that a trial's interventions are of high risk or unacceptable to certain groups in the general population, which might limit the trial's external validity. Therefore, consent rates should be a routine part of the reported literature and therefore added to the CONSORT statement to ensure that trial reports are clear, complete, ethical, and transparent.

Among phase III and IV trials, those that required at least one blood sample had higher parental consent rates than trials that did not require blood samples. We conclude that blood sampling, including painful heel sticks, might not deter parents from consenting infants to randomized phase III drug trials because the perceived benefits of a new treatment option outweigh the risk and pain associated with blood sampling. Blood sampling might also be more common in trials that enroll critically ill infants who have already undergone invasive procedures and therefore the parents perceive a lower additional cost to the study procedures.

Our study has limitations based on design and practical constraints. Our results are limited by inclusion bias, as not all authors who were contacted for additional information replied to the request. Investigators with complete consent rate data might have been more likely to respond to requests for information than investigators without complete consent rate data. Second, some trials did not collect or record sufficient data to calculate parental consent rate. It may be more difficult to track or locate parental consent data for lengthy trials that began many years ago compared with trials with more recent start dates, which prevent us from addressing changes in parental consent rate as a function of time. Our results show that study length influences parental consent rates. Therefore, there may be bias in our data if parental

consent rates in lengthy trials with early start dates are underreported. Our study design is subject to the potential for publication bias. Trials with positive results are often reported in the literature; however, negative trials or trials that are terminated early are underreported.¹⁸ These underreported trials may have a median parental consent that differs from completed, published trials. Trials that measure the safety of newer, riskier drugs may be terminated early or have poor enrollment due to hazardous side effects; therefore, these trials might be underrepresented in our sample. However, our study is the first to examine parental consent rates exclusively in the neonatal population. The review included a diverse group of subjects enrolled in trials in both academic and community centers in 19 different countries and therefore permits a more diverse determination of parental consent rate.

We found that 73% of trials reported information on the percentage of parents consented. Trial characteristics, including the use of active comparators and shorter study lengths, are associated with higher parental consent to neonatal drug trials. Future studies are needed to understand how trial characteristics, such as control type, affect parental consent. These findings may help improve the design of future clinical trials to improve participation and optimize recruitment.

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Fig. 1.
 Summary of systematic search presented as Consolidated Standards of Reporting Trials diagram.

Table 1

Study characteristics of clinical drug trials included in final review

Study characteristics (<i>n</i> = 52)	Number of trials, <i>n</i> (%)
Phase type	
1	4 (8)
2	15 (29)
3	29 (56)
4	4 (8)
Targeted gestational age	
Term and preterm	9 (17)
Only term or >2000 g	8 (15)
Only preterm	35 (67)
Drug dosing	
Single dose	14 (27)
Multiple dose	38 (73)
Blood sample collected	
Yes	38 (73)
Control type	
Standard of care/active comparator	16 (31)
Placebo	29 (56)
None	7 (13)
Maximum length of study period (includes treatment and follow-up)	
< 24 hours	2 (4)
1–7 days	4 (8)
8 days–1 month	6 (12)
1–6 months	8 (15)
> 6 months	13 (25)
Unknown	19 (37)
Funding source	
Public	11 (21)
Private	16 (31)
Public/Private	13 (25)
Maximum length of treatment	
< 24 hours	13 (25)
1–7 days	15 (29)
8 days–1 month	6 (12)
1–6 months	9 (17)
Unknown	9 (17)

Table 2

Median percentage of parental consent by trial characteristics

Trial characteristic	All trials			Phase III and IV subgroup		
	<i>n</i>	Median % parental consent (IQR)	<i>p</i> -Value	<i>n</i>	Median % parental consent (IQR)	<i>p</i> -Value
Phase	I	3 92 (70, 100)	0.36			
	II	11 72 (42, 90)				
	III and IV	24 79 (60, 87)				
Targeted gestational age	Term and preterm	5 81 (65, 87)	0.13	3	81 (52, 87)	0.56
	Only term or >2000 g	8 88 (76, 99)		4	89 (65, 99)	
	Only preterm	24 73 (59, 86)		17	74 (62, 83)	
	Yes	33 77 (62, 88)				
Randomization	No	5 84 (65, 92)	0.48			
	IV/IM	28 76 (57, 90)		16	80 (58, 87)	0.6
Drug administration route	PO/Inhaled	10 79 (62, 84)	0.9	8	76 (60, 81)	
	Single	13 80 (62, 89)		9	80 (73, 87)	0.5
Drug dosing	Multiple	25 77 (62, 88)	0.8	15	77 (57, 86)	
	Yes	26 82 (65, 91)		13	83 (74, 88)	<0.05
Blood sample collected	No	12 67 (51, 81)	0.07	11	62 (50, 80)	
	Yes	29 81 (65, 90)		15	81 (73, 88)	0.06
Direct body fluid/tissue collected	No	9 62 (52, 80)	0.08	9	62 (52, 80)	
	Standard of care/Active comparator	11 87 (83, 90)		9	87 (83, 89)	<0.05
Control type	Placebo	23 72 (52, 80)	<0.05	15	72 (52, 80)	
	None	4 79 (54, 96)		0		
Maximum length of study treatment	<24 hours	12 81 (62, 94)	0.66	9	81 (80, 89)	0.12
	1–7 days	9 72 (62, 84)		3	59 (34, 83)	
	8 days–1 month	4 79 (75, 86)		3	77 (72, 80)	
	1–6 months	5 63 (57, 70)		3	57 (32, 63)	
	Unknown	8 80 (57, 83)		6	80 (62, 88)	
Funding source	Public	7 62 (35, 70)	0.16	2	47 (32, 62)	0.39
	Private	13 80 (63, 88)		11	80 (57, 88)	

Trial characteristic	All trials			Phase III and IV subgroup		
	<i>n</i>	Median % parental consent (IQR)	<i>p</i> -Value	<i>n</i>	Median % parental consent (IQR)	<i>p</i> -Value
Maximum length of study period	10	80 (72, 92)	<0.05	5	77 (73, 81)	<0.05
	8	84 (78, 88)		4	78 (63, 84)	
	1	100 (100, 100)		0	–	
	3	84 (65, 90)		0	–	
	5	93 (92, 99)		3	99 (80, 100)	
	5	70 (63, 80)		3	80 (63, 81)	
	8	53 (33, 60)		5	50 (34, 57)	
	16	82 (73, 88)		13	81 (73, 87)	

Abbreviations: IQR, interquartile range; IV/IM, intravenous/intramuscular; PO, per os.