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Recruitment in pediatric clinical research was influenced by study characteristics and pediatricians' perceptions: a multicenter survey

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Abstract

Objectives: The aim of this survey was to quantify refusal rates and identify factors of refusal pertaining to studies and recruiting pediatricians in the research recruitment process.

Study Design and Setting: We performed a cross-sectional survey on all clinical studies conducted in six pediatric Clinical Investigation Centers in France over an 18-month period. Data were retrieved using a data collection form for the characteristics of each of the studies included in the survey and a questionnaire addressed to recruiting pediatricians. Multilevel models were used for the statistical analysis.

Results: Overall, 145 pediatricians approached the families of 999 children and adolescents for participation in 44 studies. In the 36 of the 44 studies that enrolled subjects, median refusal rate was 12.5% (Q1−Q3, 0−28%). Lower refusal rates were associated with therapeutic drug use as the focus of the study [odds ratio (OR), 0.51; 95% CI: 0.25, 1.05], additional hospital stays required for the study (OR, 0.53; 95% CI: 0.28, 0.99), longer duration of the inclusion visit (OR, 0.93/10 min; 95% CI: 0.87, 1), and recruitment by a pediatrician with university teaching responsibilities (OR, 0.26; 95% CI: 0.10, 0.68). Refusal rate was higher when the recruiting pediatrician perceived the study as generating heavy practical burden for the subject and/or its family (OR, 1.3; 95% CI: 1.17, 1.45).

Conclusion: Refusal to participate in clinical research was low and was influenced by factors associated to the objectives and conduct of the studies and factors related to the characteristics and perceptions of the recruiting pediatricians.

Keywords: Recruitment; Pediatrics; Participation; Refusal rate; Clinical research; Pediatrician perception

1. Introduction

One of the main challenges in clinical research is the recruitment of eligible participants [1,2], and children are generally considered more difficult to recruit than adults [3,4]. Reasons for this include the low prevalence of some pediatric diseases and the need to obtain written informed consent from both parents while respecting the child's autonomy [5]. However, recent studies suggest that many pediatricians may be reluctant to invite families to participate

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What is new?

Key findings

- Median refusal to participate in pediatric clinical research was 12.5% (Q1−Q3, 0−28%).
- Therapeutic drug use as the focus of the study, longer duration of the inclusion visit, and recruitment by a pediatrician with university teaching responsibilities were associated with a lower probability of refusal to participate.
- Refusal rate was higher when the recruiting pediatrician perceived the study as generating heavy practical burden for subjects and/or families.

What this adds to what was known?

- Survey findings contradict the common suggestion that children and their parents may be reluctant to participate in research.
- Use of multilevel models allowed assessment of relationships between refusal to participate and several explanatory variables while accounting for interindividual correlations within the same study.

What is the implication and what should change now?

- Implementation of pediatric studies should not be discouraged by concerns about subject refusals.
- Recruitment in pediatric clinical research can be improved by
  - enhancing the involvement of pediatricians with university teaching responsibilities in the recruitment process,
  - raising awareness among pediatricians about the importance of dedicating time to the research inclusion process, and
  - promoting the involvement of recruiting pediatricians in the early stages of study conception.

in research and that several aspects of the design and conduct of research may influence their referral behavior [6−9]. In a previous qualitative study, recruiting pediatricians reported failing to invite eligible participants because of ethical concerns or anticipated subject refusal [10]. Pediatricians' input to the recruiting process is of great concern as most families and children consent to take part in clinical research when invited to participate [11,12], and their decision is strongly dependent on the recommendations of their physician [13−16].

Evaluation of parents' and children's perspectives on research participation has been extensively addressed in the literature, and parents' psychology or personal perception of research is potentially difficult to change. Conversely, little attention has been granted on quantifying the impact of study characteristics and recruiting pediatricians' views on participation rates. Moreover, to our knowledge, participation rates have never been quantified across a large spectrum of research fields and age groups in pediatrics. Thus, the principal aim of this survey was to determine refusal rates in pediatric clinical research. We also sought to examine the relationship between study and recruiting pediatricians' characteristics and participation decisions.

2. Methods

2.1. Participants and procedures

We performed a cross-sectional survey on clinical research studies conducted in six pediatric Clinical Investigation Centers (CICs) in France (Paris, Lille, Nantes, Strasbourg, Lyon, and Marseille) between February 2006 and August 2007. The CICs are academic departments that conduct most of the pediatric clinical research performed in university-affiliated hospitals in France [17]. All studies ongoing in the six CICs during the survey period were included, regardless of study objectives and design. The recruiting physicians were pediatricians and pediatric subspecialists who practiced in university-affiliated hospitals. Subjects and families were given consent information and were invited to participate by one of the recruiting pediatricians according to a predefined study-specific procedure. Those who agreed to participate signed a written consent specific to each study.

When families were given consent information for each included study, they were also given oral information about the survey by the research team. In accordance with French laws, no written form was required for the survey. The survey was approved by the Institutional Review Board of the Paris North Hospitals, Paris 7 University, APHP (Comité d'Evaluation de l'Ethique des projets de Recherche Biomédicale du GHU Nord, n° IRB00006477, decision n° 10072).

2.2. Measures

A data collection form was used to retrieve the characteristics of the potential participants and those of the study, and this form was completed by a clinical research assistant. Also, a questionnaire was directly addressed and completed by recruiting pediatricians to assess their personal characteristics and perceptions.

When families and subjects were invited to participate in one of the included studies and were informed about our survey, the data collection forms were completed based on medical records and study protocols. Information on subjects and families included age and sex of the subject, date of the invitation to participate, participation decision (consent or refusal),

and date of the participation decision. The following information on each included study was collected: subject area, nature of sponsoring (publicly funded institution or pharmaceutical industry), number of participating centers, number of subjects initially expected to be invited for participation, number of recruiting pediatricians, study design (randomization and control group interventions), recruitment of healthy subjects and/or of disease-affected subjects, underlying disease of participants if any, and duration of the recruitment period. The included study subject area was defined as "therapeutic" when the study objective was to evaluate the therapeutic use of a drug and as "other" when the study objective was to assess the mechanisms, natural history, prognostic factors, genetics, or epidemiology of a disease. Long-lasting or recurrent underlying diseases were categorized as chronic (e.g., sickle cell disease, cancer, and genetic disorders) or not. We further recorded whether the study required additional blood samples (with three categories: none, one, and more than one), invasive investigations, visits, and/or hospital stays compared with standard care. We documented the number of pages of the case report form (CRF) to be completed for each subject participating in the study.

The questionnaire was completed directly by the recruiting pediatricians at the end of the survey and was distributed electronically. They provided demographic information, specified their role in the study (principal investigator or coinvestigator), and indicated whether they had teaching responsibilities in the university to which their institution was affiliated. They also specified whether they were providing care to the child invited to participate or met the families only as part of the study recruitment process. They were also asked to report the mean duration of each inclusion visit (defined by the mean time required to screen subjects, explain the study to potential participants, and complete required study documents for subject inclusion) and whether support staff was available to help screen subjects and complete the CRFs. Financial incentives defined as financial remuneration of the pediatrician for study participation or remuneration intended to his research team or hospital unit were noted. Financial incentives for participants in pediatric clinical research are prohibited in France. Finally, pediatricians were asked to describe their perception of the study by completing items addressing seven domains: (1) scientific interest, (2) interest for medical practice, (3) practical burden of the study for the child and/or family (additional visits and expenses), (4) inconvenience to participants related to additional procedures (blood sampling and invasive investigations), (5) potential therapeutic benefit for participants, (6) potential benefit for participants in terms of follow-up, and (7) potential research-related risks to participants. Responses to items were given using a 0−10 Likert scale (0, low and 10, high).

All information retrieved concerned factors that have been described as potentially related to recruitment rates in the existing medical literature on pediatric research recruitment [4,7,10].

2.3. Statistical analysis

Descriptive data included absolute numbers (percentages) for categorical variables and medians [first (Q1) and third (Q3) quartiles] for continuous variables.

Multilevel models, accounting for interindividual correlations within the same study, were used to assess relationships between refusal to participate and several explanatory variables [18]. Such models are applied to analyze data from units grouped at different levels. To preserve recruiting pediatricians' anonymity, neither the identity nor the number of families invited by each pediatrician was known, and consequently, the subject level could not be fitted into the pediatrician level. Therefore, the characteristics of the recruiting pediatricians for each study were summarized as means or percentages, which were included in the study level, together with the study characteristics. For the analysis, levels were defined as shown in Fig. 1. During analysis, we observed a nearly fivefold difference in the number of subjects included in the largest study and the second largest study ($n = 413$ and $n = 84$, respectively). As large-size imbalances may have a major influence on statistical results, we included only the data from the first 84 families invited to participate in the largest study. Thus, a total of 670 decisions were analyzed. Nevertheless, a sensitivity analysis was conducted, and the final model obtained as aforementioned was compared with the model obtained using all available data ($n = 999$).

The multivariate analysis included the variables that were significantly associated with refusal to participate in the bivariate analysis. A backward−forward stepwise approach was used for multivariate model selection. All tests were two sided, and the significance threshold was 10% for both the bivariate and the multivariate analyses. Results are reported as odds ratios with 95% confidence intervals. Descriptive analyses were performed using SAS, version 9.2 (SAS Inc., Cary, SC, USA), and the multilevel model analysis using MLwiN, version 2.02 (Multilevel Models Project, Institute of Education, University of Bristol, UK).

3. Results

3.1. Participants and invitations to participate

The parents or legal guardians of 999 eligible subjects were approached regarding consent to participation in 1 of the 44 ongoing studies.

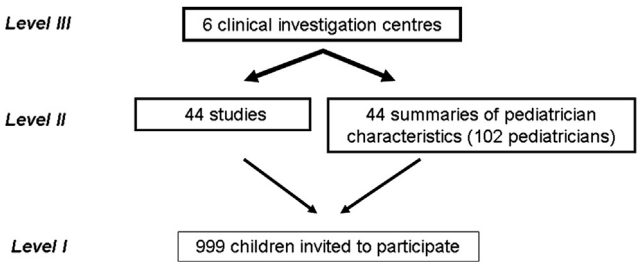

Fig. 1. Multilevel modeling analysis.

Table 1 reports the characteristics of the studies and Table 2 reports those of the subjects. Most of the studies were multicenter studies ($n = 36$, 82%), conducted nationwide ($n = 34$, 87%), and sponsored by publicly funded institutions ($n = 31$, 70%). Approximately half of the studies evaluated the therapeutic use of a pharmaceutical intervention; however, only eight (18%) were placebo controlled. Participation in studies concerned mainly adolescents, subjects who presented chronic diseases ($n = 28$, 64%), and involved no additional procedures except blood sampling (Tables 1 and 2). Study-related workload was relatively high, based on the large number of CRF pages, whereas the median number of recruiting pediatricians was small (Table 1).

Table 1. Characteristics of the 44 studies

Study characteristics ($n = 44$)	Total, median (Q1–Q3) or number (%)
Nb of centers	
One center in France	8 (18)
>1 center in France	26 (59)
International	10 (23)
Sponsoring	
Public	31 (70)
Private	13 (30)
Subjects	
Healthy subjects ± disease-affected	6 (14)
Disease-affected only	38 (86)
Underlying disease	
Chronic	28 (64)
Not chronic	16 (36)
Subject area	
Therapeutic	19 (43)
Other areas	25 (57)
Study design	
Randomized controlled study	16 (36)
Controls with usual care	1
Controls with reference drug	7
Controls with placebo	8
Controlled study without randomization	7 (16)
Observational, not controlled study	21 (48)
Blood sampling	
No additional	11 (25)
1 additional	8 (18)
>1 additional	25 (57)
Invasive tests	
No	38 (86)
Yes	6 (14)
Additional visits	
No additional	19 (43)
1 additional	8 (18)
>1 additional	17 (39)
Additional hospital stays	
No	30 (68)
Yes	14 (32)
Nb of CRF pages	31.5 (20.5–49.5)
Nb of recruiting pediatricians per study	2 (1–4)
Duration of recruitment (mo)	10.1 (6.8–12)
Nb of subjects invited	8 (2.5–20)
Nb of subjects invited/expected (%)[a]	97 (22–171)
Refusal (%)	12.5 (0–28)

Abbreviations: Nb, number; CRF, case report form.

[a] Ratio of the number of subjects invited to participate on the number of subjects initially expected to be invited for participation.

Table 2. Characteristics of the 999 subjects invited to participate in research studies

Characteristics of subjects ($n = 999$)	Total, median (Q1–Q3) or number (%)
Sex[a]	
Male	492 (49)
Female	501 (50)
Age (yr)	13.4 (4.5–14.8)
Newborns (<28 days)	146 (15)
Infants (28 days to <2 yr)	74 (7)
Children (2 to <12 yr)	150 (15)
Adolescents (12 to <18 yr)	629 (63)

[a] missing = 6 data.

3.2. Recruiting pediatricians

Of the 145 pediatricians declared as recruiting pediatricians in the 44 studies, 102 (70%) completed the questionnaire (Table 3). No pediatrician participated in more than one study. Most of them were declared as coinvestigators in the study ($n = 84$, 82%), with teaching responsibilities ($n = 52$, 51%) and were the subject's principal medical care providers ($n = 66$, 65%). Presence of a support staff was common; however, few recruiting pediatricians reported financial incentives ($n = 23$, 23%). Studies were globally perceived as scientifically and medically interesting and as involving a potential therapeutic benefit for participants (Table 3). Recruiting pediatricians acknowledged a practical burden for families and participants as a result of study participation, although median scores for perceived inconvenience related to study procedures and potential research-related risks were low.

3.3. Refusal rate

The median period of recruitment in the evaluated studies was 10.1 months (Table 1). In 8 (18%) of the 44 studies, no subjects had been invited to participate; thus, these studies were excluded for further analyses. Only 11 (11%) of the 102 recruiting pediatricians who completed the questionnaire participated in these studies. In the remaining 36 studies, the median number of subjects invited to participate was 8 (3–20), and the median ratio of invited subjects to the number of subjects initially expected to be screened for participation was 97%.

Median refusal rate among the 36 studies with recruitment was 12.5% (0–28; Table 1), and rates varied widely across studies. Interestingly, in 16 (44%) of 36 studies, no refusals were recorded. The median time between the date of the invitationand the date of the participation decision was 2 days (range, 0–268 days). The families indicated their decision on the day of the invitation for 390 (45%) of 858 subjects for whom this information was available and more than 10 days after the invitation for 319 (37%) of them.

Table 3. Characteristics of the 102 recruiting pediatricians

Pediatricians' characteristics (n = 102)	Total, median (Q1–Q3) or number (%)
Age (yr)	42 (37–50)
Gender	
Men	48 (47)
Women	54 (53)
Recruiting pediatricians with teaching responsibilities	
Yes	52 (51)
No	50 (49)
Role in research	
Principal investigator	18 (18)
Coinvestigator	84 (82)
Providing medical care to the child	
Yes	66 (65)
No	36 (35)
Support staff	
Yes	76 (75)
No	26 (25)
Financial incentives[a]	
Yes	23 (23)
No	79 (77)
Mean duration of inclusion visit (min)	60 (30–90)
Scientific interest (0–10)	8 (7–9)
Interest for medical practice (0–10)	8 (5–9)
Practical burden of the study for the child and/or family (0–10)	6 (3–8)
Inconvenience to participants related to additional procedures (0–10)	4 (2–7)
Potential therapeutic benefit for participants (0–10)	7 (2–8)
Potential benefit for participants in terms of follow-up (0–10)	5.5 (2–8)
Potential research-related risks for participants (0–10)	1 (0–2)

[a] Remuneration of the pediatrician for study participation or remuneration intended to his research team or hospital unit.

3.4. Factors associated with refusal to participate

In the bivariate multilevel analysis, 10 variables were independently associated with refusal to participate (Table 4) and were subsequently included in the multivariate multilevel analysis. No effect of age on refusal to participate was identified. The final model was further adjusted to the presence or absence of a chronic disease. In this model, five variables influenced refusal to participate. In studies with a therapeutic objective and those with additional hospital stays, families were approximately two times less likely to refuse participation. Probability of refusal also decreased by 74% when the recruiting pediatrician had teaching responsibilities and by 7% for every 10 additional minutes of the mean duration of the inclusion visit. However, the more recruiting pediatricians perceived the practical burden of the study as high, the more likely subjects and families were to refuse participation, with an increase of 30% in the probability of refusal for every additional point in the Likert 10-point scale. Of note, the nature and effects of these five variables remained unchanged when the data from all 999 subjects were analyzed (data not shown).

4. Discussion

To our knowledge, this is the first survey to quantify participation refusal rates across a large spectrum of research studies and age groups in pediatrics and explore the relationship between participation rates and research characteristics.

The median refusal rate of the 36 studies evaluated in this survey was 12.5% (0–28), which is lower than that in previous studies in which children's and adult's willingness to participate varied between 50% and 80% [11,14,19–21]. Because participation rates have been described as potentially influenced by the presence of severe chronic diseases like pediatric cancers [4], we adjusted our multivariate analysis for the presence of a chronic disease. In more than one-third of the studies in our survey, there were no refusals. These findings contradict the common suggestion that children and their parents may be reluctant to participate in research [22,23]. They also indicate that the decision is influenced by the importance of the study question and recruiting pediatricians' perceptions. We found significantly lower refusal rates for therapeutic drug trials and studies requiring additional hospital stays. The latter could be a proxy for a significant improvement in the child's medical care. For example, the opportunity to access new treatments could be a major incentive to consent to research that outweighs concerns about inconvenience to participating families. Studies with direct therapeutic benefits to patients also receive stronger support from physicians in terms of subject enrollment [6,8].

Families who were invited to participate by a pediatrician with teaching responsibilities consented more often than families invited by nonteaching pediatricians. We used teaching status as a surrogate for research experience and time spent in research activities, two factors previously reported to be related to patient recruitment [7,9,24]. Pediatricians with teaching responsibilities are more likely to acknowledge previous experience in clinical research and benefit from time specifically allocated to research as these are both requirements for and consequences of their teaching status. Thus, they have a better understanding and acceptance of research procedures. Furthermore, a longer inclusion visit was associated with a lower refusal rate in our survey. Previous studies showed that the concern about information and the consent process was a major barrier to research participation of children and adults [4,24]. Dedicating time to screen, provide consent information, and complete required inclusion documents is an essential part of the recruitment process, although clinicians report difficulties conciliating routine medical practice and research workload [6,7]. Our findings suggest that time constraints may require pediatricians to refrain from inviting potential research participants or to shorten the study information provided to families, eventually leading to participation refusals.

In our survey, recruiting pediatricians' negative perception of the practical burden placed by the study on the child

Table 4. Factors that influenced refusal to participate in pediatric clinical research (n = 670 decisions concerning participation)

	Bivariate analysis			Multivariable analysis[a]		
Variables	**OR**	**95% CI**		**OR**	**95% CI**	
Subject area						
Therapeutic	0.45	0.22, 0.94	*	0.51	0.25, 1.05	**
Other areas	1			1		
Randomization vs. placebo						
No	1					
Yes	0.40	0.13, 1.18	**			
Number of CRF pages	0.76	0.75, 0.78	*			
Additional hospital stays						
No	1			1		
Yes	0.47	0.23, 0.99	*	0.53	0.28, 0.99	*
Blood sampling						
No additional	1					
1 additional	0.39	0.13, 1.12	**			
>1 additional	0.87	0.38, 1.98	***			
Recruiting pediatricians with teaching responsibilities						
No	1			1		
Yes	0.35	0.11, 1.09	**	0.26	0.10, 0.68	****
Financial incentives[b]						
No	1					
Yes	0.52	0.27, 1.02	**			
Mean duration of inclusion visit (per 10 min)	0.87	0.77, 0.99	*	0.93	0.87, 1	*
Practical burden of the study for the child and/or its family (0–10)	1.37	1.19, 1.57	****	1.3	1.17, 1.45	****
Inconvenience to participants related to additional procedures (0–10)	1.19	0.98, 1.44	**			

Abbreviations: OR, odds ratio; CI, confidence interval; CRF, Case Report Form.
*≤0.05, **≤0.1, ***>0.5, ****<0.01.
[a] Final model adjusted for presence or absence of a chronic disease.
[b] Remuneration of the pediatrician for study participation or financial remuneration intended to his research team or hospital unit.

and the family influenced refusal rates. We evaluated individual opinions that may not always be in keeping with the positive opinion of the research ethics committees. Thus, pediatricians' perceptions could have influenced their behavior when interacting with families and children during consent information visits. If their perception of the study is negative, they would be more likely to provide evasive information about the study, to share negative thoughts with families, or even to discourage some from participating. Our results are in line with previous studies suggesting that recommendations of recruiting pediatricians are very important to both children and parents and that the preferences of physicians account for most of the decisions to consent to or refuse participation [10,14,25,26]. Therefore, it seems important to take into account the way a study is perceived by the recruiting pediatricians. One possible way to do that would be to involve these pediatricians at the early stages of study conception. Also, as attitudes may vary from one recruiting pediatrician to another, unequal access of subjects to research could follow. Indeed, the importance of this issue is widely underestimated. Physicians' attitudes toward research and the mechanisms through which they influence decisions of potential participants need to be further evaluated as this was beyond the scope of the present survey.

Our survey presents some limitations. Although the response rate for the recruiting pediatricians questionnaire was high (70%) compared with that of previous studies [8], missing data may have affected our findings. Also, our methodological choice of including the first 84 consecutive patients in our exploratory analysis, instead of the 84 last ones or a random sample, could also have affected the results of the survey. However, the sensitivity analysis was reassuring. In addition, we used summarized data rather than individual data to characterize recruiting pediatricians. However, we believe that preserving anonymity was crucial and that it maximized the response rate of the survey. Finally, low refusal rates in our survey could also be related to the fact that recruiting pediatricians may have invited for participation only the families that were likely to accept and not all eligible participants. Yet, this attitude is practically impossible to quantify and so is its impact on recruitment rates [10].

5. Conclusion

Certain pediatricians fail to invite eligible participants to pediatric clinical research because of anticipated subject refusal. Our survey shows that refusal to participate is not an obstacle to recruitment in pediatric clinical research and should not discourage implementation of pediatric studies. Nevertheless, recruitment for research is a highly complex process. Families are more likely to accept participation if

they are solicited by pediatricians who dedicate time for subject inclusion and have a positive perception of the practical burden imposed to families. On the other hand, a negative attitude of recruiting pediatricians when giving study consent information may jeopardize subject participation. Careful consideration of the aforementioned factors is crucial to optimize recruitment rates and equity of access to pediatric research.

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