MAR Pediatrics (2023) 4:6

Research Article

A Survey Based Comparative Study to Understand the Challenges Faced Towards Recruitment in Paediatric Clinical Trials between Site Personnel's Versus Clinical Research Professionals

Ms. Tanvi Kabre *[1], Dr. Kaushal Kapadia [2]

1. Texila American University.

2. Clinical Research Professional.

***Correspondence to:** Ms. Tanvi Kabre, Texila American University.

Copyright

Received: 21 August 2023

Published: 01 September 2023

Abstract

Children have been excluded from clinical trials for prolonged times. Most of the drugs and procedures used in children have not be tested in the prior. However, in recent times regulations and guidelines promote pediatric trials unless there seems to be considerable harm, or any specific reasons need children to be excluded. Being said recruitment of children in trials continues to be challenging. Compared to adults, enrolling children at different stages of life requires different considerations. The present rate of research participation in the present scenario is far from optimum, and it requires greater active participation from all involved parties. The study successfully identified several factors, which according to the involved stakeholders were the main reasons for low recruitment in pediatric trials in India. The participating stakeholders also expressed their ideas on how to overcome these obstacles.The responses given by the two groups were compared and a difference in the two perspectives was observed. These ideas can become instrumental in formulating novel strategies for improving the recruitment rate.

Keywords: *Site Personnel, Clinical Research Professionals, Comparative study, Paediatric Clinical trials, recruitment rates..*

Introduction

When any clinical trial is conducted for a pediatric condition and administration of novel components is performed in an off-label manner, in absence of high level of evidence it becomes of utmost importance to choose the correct control. The Declaration of Helsinki requires that treatment offered to the control group should be the current best standard treatment, and that those allocated to the experimental group receive a treatment proposed to be as good as or better than standard treatments**[**1**]**. Hence, a well-designed randomized clinical trial could arguably offer a patient the optimum treatment approach**[**2, 3**]**. However, studies that breach this provision are still sometimes done to gain regulatory approval**[**4**]**.

Over the world, if the major regulatory authorities and their recommendations are looked at, the focus for pediatric clinical trials remains on better risk-benefit ratio. However, there are certain less prioritized issues such as fear, uncertainty, and lack of awareness among the parents about clinical research, and the scientific reluctance of pediatricians to enroll eligible children in relevant trials rather than using treatments or interventions that were not studied appropriately in the children**[**5**]**. If a new drug is intended primarily for use in pediatric patients, clinical trial data should be generated specifically in that population. However, initial safety and tolerance can be derived from data obtained from studies involving adult participants, unless such initial safety studies would expose them to undue risk or provide little useful information.

There might be additional benefits for patients who receive treatment at a hospital or institution involved in clinical trials. In studies involving adults, doctors who participate in clinical trials are more likely to incorporate trial findings and published data into clinical practice**[**6**]**. Many investigations have shown that such inclusions benefit all participants of the clinical trial, including children. This is referred to as the Hawthorn effect**[**7,8**]**. Participants of clinical trials, including those assigned to placebo, have outcomes similar to or better than those of eligible non-participants. Participants often display mortality, fewer clinical events, and lower complication rates than similar patients treated outside clinical trials. This "survival advantage" is not explained by differences in pre-treatment disease status or factors of known prognostic importance**[**9**]**. In some instances, this advantage may appear as byproducts of volunteer bias, but it could also be due to closer monitoring and better care of trial participants.

Despite the potential benefits that can arise from participating in clinical trials, children may also get exposed to the risks involved. These potential risks are often specific to children and are not usually of concern when considering implementation in adults. These often include discomfort, inconvenience, pain, fear, and separation from parents or familiar surroundings, effects on growing or developing organs, and size or volume of biological samples. Realistic clinical trials, which do not impose a burden of treatment, testing, and monitoring greater than routine clinical care, are designed to prevent additional risks for trial participation**[**10**]**.

There are significant ethical issues faced by drug manufactures and health authorities in performing research in children. For global trials, sponsors must evaluate prior to trial initiation whether the disease definition is the same in the countries under consideration, and whether sample analyses and/or definitions of acceptable clinical laboratory parameters are comparable across countries. Proven safety and efficacy of drugs in the population under study are clearly the major goals of the drug development and approval

processes. However, the perspectives of the pediatric patient, the parent/guardian, health authority and manufacturer are often different and may at times be in conflict. In certain cases of clinical trials where genetic components are present, DNA analysis can become a detriment to participation. This can be particularly observed in case of objections based on religious grounds. The parent/guardian may object to either collecting a sample for genetic analysis or for retention of any part of a genetic sample. Informed consent needs to be written clearly, explaining why genetic analysis is required and ensure that samples will only be used to evaluate the condition under study as opposed to future disease risks. Gaining consent for DNA analysis can be of particular concern for evaluation of drugs where the number of individuals in the population is very low and when a protocol requires this analysis.

Methodology

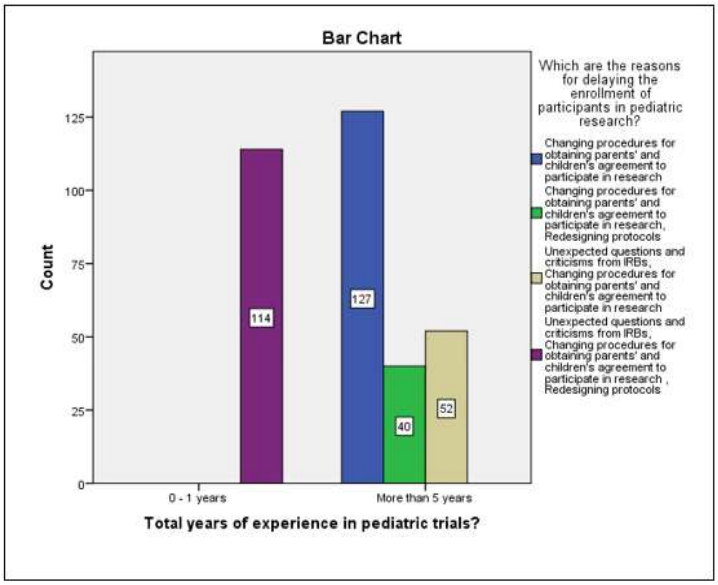
The primary objective of this research project will be to gather data on barriers and facilitators of recruitment in pediatric trials within India. This will be achieved by a questionnaire filled by industry experts from CROs or pharmaceutical companies and site personnel explaining their perspective. Data collected from these groups on low recruitment rate in pediatric trials and measures take to improve and maintain the recruitment rate would be analyzed and compared for the difference between the perspectives of two groups. A database was created with the purpose of collecting data from the respondents. The database was designed in order to provide all necessary information on objectives of the project, information on the author, confidentiality statement and consent of participant. And after completing the questionnaire the participant was required to submit the questionnaire.

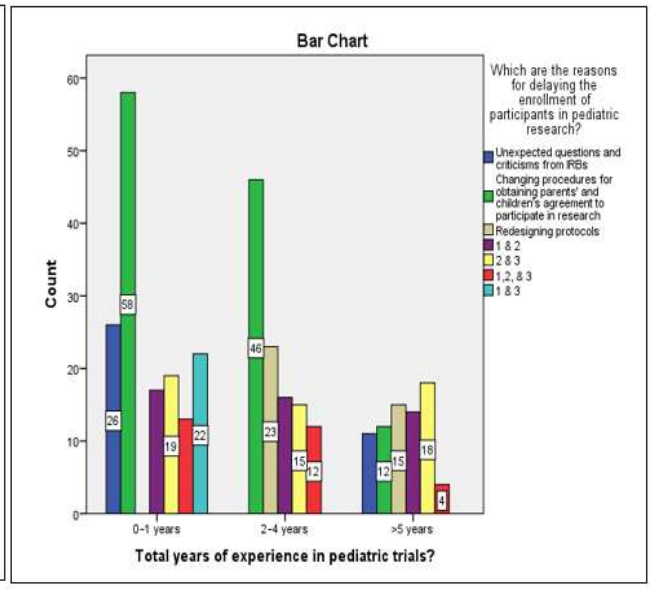
Results

The first section of the survey aimed to detail the demographics of the participants irrespective of which group they belong to. The collected data provides an overall idea about the participants, their educational qualification and further details, which were essential in understanding their choices. In the questionnaire survey, the responses of the participants were recorded and were compared with the variable of total years of experience in pediatric trials.

When the participants were asked if they were aware of any guidelines for the management of pediatric trials 66.1% of the site personnel and 51.6% of the clinical research professionals answered in negative.

Next, they were asked, what they thought were the reasons for delaying the enrollment in pediatric research. Majority of Clinical research professionals (34.0%) stated that they believed, ‘Changing procedures for obtaining parents' and children's agreement to participate in research’ was the main reason. (38.1%) of the site personnel stated that they believed, ‘Changing procedures for obtaining parents' and children's agreement to participate in research’ was the main reason. While 34.2% stated that unexpected questions and criticisms from IRBs, changing procedures for obtaining parents' and children's agreement to participate in research, and redesigning protocols were the main reason.



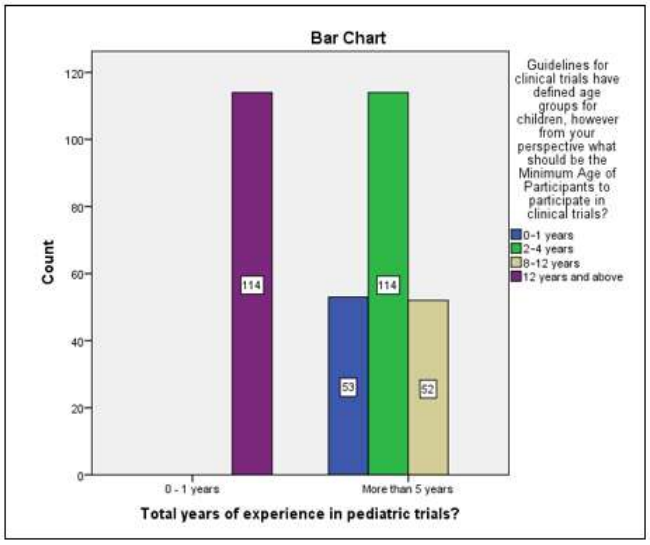


Site personnel **Clinical Research professionals**

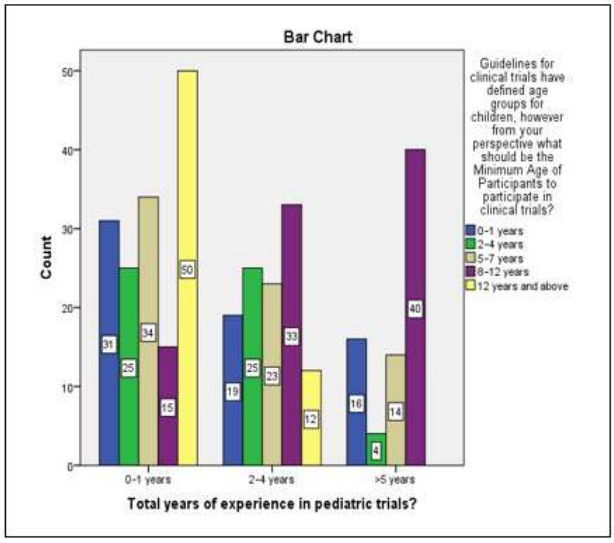
Next, the participants were asked if they thought, limited scientific literacy can in general population be responsible for narrowing the chances of patient enrollment in the trials? 27.3% of the site personnel agreed to the statement, while 72.7% strongly agreed to it. On the other hand, 49.3% of the clinical research professionals agreed to the statement, while 28.7% strongly agreed to it. The participants were then inquired if the enthusiasm from the lead investigator and friendly and approachable study coordinator can not only improve recruitment but also lower the study's dropout rate. To this 57.5% of clinical research professionals strongly agreed and 36.4% agreed to the statement. For the site research personnel, 84.1% of participants strongly agreed and 15.9% agreed to the statement.

Next, the following question was posed to the participants, ‘Guidelines for clinical trials have defined age groups for children, however from your perspective what should be the Minimum Age of Participants to

participate in clinical trials?'. To this, 15.6% of the site personnel stated that minimum age should be between 8 to 12 years, 34.2% stated that it should be between 2 to 4 years, and 34.2% stated that it should be more than 12 years. For the Clinical Research professionals, 25.8% stated that minimum age should be between 8 to 12 years, 20.8% stated that it should be between 5 to 7 years, and 18.2% stated that it should be more than 12 years.



Site personnel



Clinical Research professionals

Then the participants were asked, which are the common ethical and regulatory barriers stated by site personnel for denying the conduct of pediatric trials and thus leading to low recruitment? To which, 11.7% site personnel and 27.6% of research professionals stated that addressing IRB questions and concerns, was the major barrier. 38.1% site personnel and 20.8% research professionals stated that the barrier was obtaining parental consent.

When the participants were asked, 'Investigators have not been adequately educated about the special regulatory protections for children and can result in low recruitment in the trial?', 65.8% of the site personnel and 53.7% of research professionals agreed to the statement, while 34.2% of site personnel and 29.9% of research professionals strongly agreed to the statement.

Next, in response to the question, 'The extended time required to gain IRB approval for pediatric studies is one of major reason for low recruitment rate?', majority of the site personnel (65.5%) believed the statement to be false, while 34.5% believed it to be true. In case of research professionals, the opposite was observed,

majority (58.9%) believed the statement to be true, while 41.1% believed it to be false.

Next the participants were asked, if 'Protocol design and strict inclusion/exclusion criteria is known to narrow the recruitment rate in pediatric trials?'. To which 27.6% of the site personnel and 53.4% of the research professionals stated they agreed to the statement, while 44.7% of the site personnel and 27.6% of research professionals strongly agreed. The participants were then asked, if the duration of clinical trial and number of visits was responsible for lower recruitment. To which 50.2% of site personnel and 55.4% of research professionals agreed and another 22.5% of site personnel and 27.9% of research professionals stated they strongly agree.

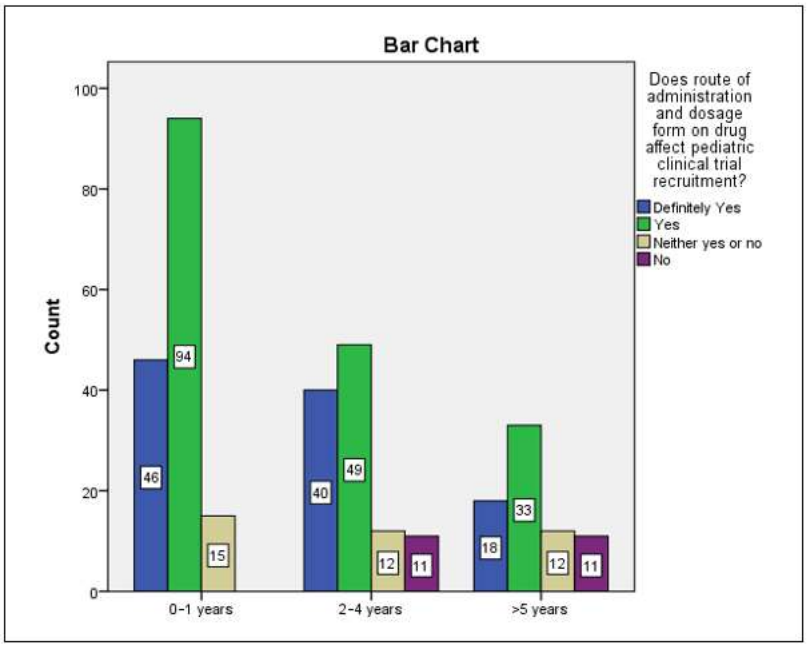
The participants were then inquired, if expanding the number of study centers can help to combat low enrollment? To which 56.8% of the site personnel strongly agreed and 51.3% of the research professionals strongly agreed. Next, the participants were asked, 'To what extent does inform consent and assenting process impact pediatric recruitment?'. To this question, 50.2% of site personnel and 40.8% of research professionals stated that it was high.

The participants were then asked, 'Does route of administration and dosage form on drug affect pediatric clinical trial recruitment?' 33.9 % of site personnel and 51.6 % of research professionals responded yes, and 66.1% of site personnel and 30.5% of research professionals replied definitely yes.

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.006[a]	1	.939		
Continuity Correction [b]	.000	1	1.000		
Likelihood Ratio	.006	1	.939		
Fisher's Exact Test				1.000	.516
N of Valid Cases	333				
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 38.68.					
b. Computed only for a 2x2 table					

Site personnel

Chi-Square Tests of 'Does route of administration and dosage form on drug affect pediatric clinical trial recruitment' Vs. 'Total years of experience in pediatric trials'



Discussion

The current thesis thus investigates which factors are involved in shaping the outlook of the personnel who have been actively involved in pediatric clinical trials. It sheds new light on understanding the perspective, strategies, issues from different groups viz. Clinical Research Professionals working with CROs / Sponsor; PI, Sub-I & CRC from clinical trial sites.

Members from these two groups were first asked, if they were aware of the any guidelines for the management of pediatric trials. In response it was revealed that there was considerable lack of awareness among both the groups. However, in case of CRO's more than 50% of the participants admitted that they were unaware of any such guidelines. In case of site personnel, this number was a bit higher, being greater than 60%. The participants from these groups, who answered in 'yes', were then asked to name at least one of such guidelines, many of them were able to correctly name the policy forming guidelines, such as ICH E11, ICH GCP and ICH Clinical Investigation of Medicinal Products. Level of awareness was not shown to increase with experience in both cases of CROs and site personnel. This is somewhat counterintuitive to previous report. One report had observed that level of awareness increased with increase in clinical work experience of 10-20 years**[**11**]**. The report stated that personnel who were in higher authorities displayed

greater knowledge on the matter. No such significant deviation was observed in the present study.

The success of any scientific method is dependent on the expertise of the people involved in its undertaking. The experience gathered by those who work with children at clinical trials can be a treasure trove of information. This repository of information along with the valuable insight of the personnel involved can generate much understanding about how society views the participation of children in clinical trials. In the present study, participants from both groups, the CROs and site personnel, were first asked to self-evaluate by asking them what would be the impact on clinical trials if the personnel involved were not properly experienced. About 90% of site personnel stated that this will impact the study, and the same type of response was observed from the CROs. This revealed that both groups valued the fact that personnel involved in the clinical trials should have a clear understanding of the protocols and hesitation / concerns on the study. Participating or being involved with a study without having the basic knowledge about it can lead to a deep negative impact on the investigation as a whole. Both the groups identified this. Responses were more mixed in nature when participants from both groups were asked how much experience should a Principal Investigator (PI). But most participants from both groups agreed that it should be more than 5 years. The importance of experience cannot be overstated in any clinical study. Therefore it is quite understandable why the respondents preferred that PIs should be more experienced.

Whatever trial has been conducted, has mostly been restricted to some childhood diseases, heavily clustering around cancer. Consequently, many ineffective and even harmful interventions are used in children before they have been appropriately assessed in randomized trials**[**12**]**. Majority of the medical professionals agreed that changing procedures for obtaining the consent of parents and children is the prime reason for delay in clinical trials. Therefore it can be stated that coming up with a standard guideline for proper design and conduct of pediatric clinical trials can speed up the time required for the completion. Another major cause behind the low number of studies is the low rate of enrollment. Almost 50% of CROs stated that they believed limited scientific literacy can in general population be responsible for narrowing the chances of patient enrollment in the trials. This belief was much lower in case of site personnel. However, if it is indeed true, then it is absolutely necessary to take steps to ensure the spread scientific literacy.

Age of the children participating in clinical trials is also a major factor that controls the quality of research in pediatric clinical trials. When asked about the appropriate age of participation in clinical trials, there was some difference of opinion among the two groups of professionals involved. Among the site personnel involved in clinical trials, the majority were equally divided. While one half believed that children should

be allowed to participate at an earlier age of two to four years, the other half opined that the children should be more than twelve years of age before participating in any clinical trials. The group of CROs and sponsors were also in the favor of the children being more than twelve years of age. This was due to the fact that assent from participating children is a major component of pediatric clinical trials. The involved research personnel should perform an assessment of the child's understanding of the information provided and the influences that impact on the child's evaluation of the situation**[**15**]**. In low- and middle-income countries similar to India, poverty, fear of exploitation, and mistrust represent additional challenges**[**12**]**. However, clinical research involving children is essential for advancing child health**[**13**]**. Without sound drug studies in children, children may not benefit from and may even be harmed by drugs with an indication for use in adults**[**14**]**.

Conclusion

The present study was conducted through a questionnaire survey involving parents, sponsors and site personnel with focus on issues persisting with recruitment and recruitment rate in pediatric clinical trials and comparing the two perspectives. To this end the study successfully identified several factors, which according to the involved stakeholders were the main reasons for low recruitment in pediatric trials in India. The participating stakeholders also expressed their ideas on how to overcome these obstacles. These ideas can become instrumental in formulating novel strategies for improving the recruitment rate. The imperative to undertake clinical trials in children arises from extraordinary advances in the modern-day understanding of basic biomedical sciences. These clinical trials require a matching commitment to translational research if child health is to utilize the gains from these new findings. Unfortunately, many prescribed treatments for children remain yet to be adequately tested in children. This can sometimes lead to the administration of harmful treatments while withholding beneficial treatments. The pool of eligible children entering trials is often small because many conditions are uncommon in children, and the threshold for gaining consent is often higher and more complex because parents have to make decisions about trial participation on behalf of their child. Uncertain about what is best, despite supporting the notion of trials in principle, parents and pediatricians generally opt for the new intervention or for standard care rather than trial participation.

Reference

1. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama. 2013 Nov 27;310(20):2191-4.

2. Segelov E, Tattersall MH, Coates AS. Redressing the balance-The ethics of not entering an eligible patient on a randomised clinical trial: Point of view. Annals of oncology. 1992 Feb 1;3(2):103-5.

3. Kerr D. World summit against cancer for the new millennium: the Charter of Paris. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2000 Mar 1;11(3):253-4.

4. Michels KB, Rothman KJ. Update on unethical use of placebos in randomised trials. Bioethics. 2003 Apr;17(2):188-204.

5. Khan-Boluki J, Hundt F. Kinder in klinischen Studien: Umfrage zur Situation in universitären Kinderkliniken in Deutschland. GMS German Medical Science; Germany; 2008; Vol. 6, ISSN 1612-3174.

6. Ellis PM, Buttow PN, Simes RJ, Tattersall MH, Dunn SM, MacLeod C. Doctors' participation in randomized trials of adjuvant systemic therapy in breast cancer: how does it relate to their recommendations for standard therapy in breast cancer?. The Breast. 1999 Aug 1;8(4):182-7.

7. Vist GE, Hagen KB, Devereaux PJ, Oxman AD. Outcomes of patients who participate in randomized controlled trials versus those of similar patients who do not participate (Protocol for a Cochrane Review). The Cochrane Library. 2001(4).

8. Schmidt B, Gillie P, Caco C, Roberts J, Roberts R. Do sick newborn infants benefit from participation in a randomized clinical trial?. The Journal of pediatrics. 1999 Feb 1;134(2):151-5.

9. Davis S, Wright PW, Schulman SF, Hill LD, Pinkham RD, Johnson LP, Jones TW, Kellogg Jr HB, Radke HM, Sikkema WW, Jolly PC. Participants in prospective, randomized clinical trials for resected non-small cell lung cancer have improved survival compared with nonparticipants in such trials. Cancer. 1985 Oct 1;56(7):1710-8.

10. Roland M, Torgerson DJ. Understanding controlled trials: What are pragmatic trials?. Bmj. 1998 Jan 24;316(7127):285.

11. Kumar R. The perceptions of medical doctors on clinical research ethics in Lithuania and India.

12. Caldwell PH, Murphy SB, Butow PN, Craig JC. Clinical trials in children. The Lancet. 2004 Aug 28;364(9436):803-11.

13. MacLeod SM, Knoppert DC, Stanton-Jean M, Avard D. Pediatric clinical drug trials in low-income countries: key ethical issues. Pediatric Drugs. 2015 Feb;17:83-90.

14. 9. Medical Research Council (Great Britain). MRC Ethics Guide: Medical research involving children. Medical Research Council; 2004.

15. Grimsrud KN, Sherwin CM, Constance JE, Tak C, Zuppa AF, Spigarelli MG, Mihalopoulos NL. Special population considerations and regulatory affairs for clinical research. Clinical research and regulatory affairs. 2015 Apr 3;32(2):45-54.