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Research Article

A Survey Based Study on Understanding Challenges Towards Recruitment in Paediatric Clinical Trials: A Site Personnel's Perspective

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Abstract

Research and subsequent clinical trials involving human subjects have often been controversial and have been long associated with a not-so-glorious legacy. Children represent an especially vulnerable population with developmental, physiological and psychological differences from adults, which make age- and development-related research important for their benefit. Therefore, it is important to ensure that clinical trials involving children are conducted with the highest ethical standards and prioritize their safety and well-being. A clinical investigation involving children is always a complex chain of decision-making in many facets. The presented work sheds new light on understanding the perspective, strategies, and issues from PI, Sub-I & CRC from clinical trial sites. The obtained results revealed many details regarding what factors control the level of participation among the Indian population. Obtaining parental consent appeared as a major cause of low recruitment, along with protocol design and strict inclusion/exclusion criteria. Among other factors that were considered to be limiting the number of participants were, the duration of the clinical trial and the number of visits required, study intervention and indication of the drug, route of administration, and dosage form of drug.

Keywords: *Pediatric trials in India, recruitment rates, site personnel.*

Introduction

Clinical trials involving children has always been ethically problematic. The fundamental reason for this being quite direct. Clinical research, by its very nature, uses subjects as a means to the end of creating generalizable knowledge. In adults, the solution to this fundamental ethical problem is to acquire the voluntary, informed consent of the research subject. Children cannot consent on their own behalf. Instead, researchers, parents, and regulators must determine whether the risk-benefit ratio is acceptable in order to permit the research to go forward. While understanding the reasons for extra scrutiny of pediatric clinical trials are straightforward, the arguments for the necessity of doing research in children are also compelling.

Children, and particularly infants, respond differently to drugs and other medical treatments as compared to adults. There are multiple instances of drugs that, while behaving safely in adults, have serious and even fatal side effects in children1. Therefore, trials involving children often necessitate longer follow-ups than do studies involving adults. This is done in order to determine whether innovative treatments have any long-term developmental effects.

Despite having long-term potential benefits, clinical trials involving children are few and far between. Unfortunately, as there are few pediatric trials [2], the list of improvements in child health resulting from such clinical trials is also very limited and is often restricted to certain pediatric diseases. Most of which are focused around cancer. The limited number of clinical trials mean that many ineffective and even harmful interventions get used in children before getting appropriately assessed in randomized trials[3,4]. In other scenarios, where interventions are effective they have had a delayed introduction into practice. In the absence of specific trial-based data in children, clinicians, families and policy-makers are forced to extrapolate from results of studies in adults. Such extrapolations are often inappropriate because children have a different range of diseases and metabolize medications differently. This may often result in responses to treatment that are unpredictably different to adults [1,3,4].

The medical investigator was considered the sole authority that could adjudicate the legitimacy of a study protocol, even as recently as the 1970s. Even in more recent times, clinical trials involving children have failed to provide adequate protection to the participants. The safety and wellbeing of participating patients was generally considered to be warranted by the commitment of physicians, by the Hippocratic Oath, to ‘do no harm’ to their patients. The necessity of a research ethics distinct and independent from medical ethics emerged only in the moment these episodes of research misconduct exposed such conviction in all its inadequacy. The effort of medical research often presents the physicians and investigators with unprecedented ethical dilemmas. In most cases, the physician is bound by his or her professional ethics to do all that is in his or her power to benefit the current participant. On the other hand, though, the investigator is also burdened with the obligation to forward medical science for the benefit of future cases. The necessity of a framework for critically discussing and evaluating human experimentation arises because the tools of medical ethics alone are often insufficient to direct a course of action in the face of such a dilemma. The course of action for an investigator often comes down to his or her personal predicaments. An investigator, personally more inclined towards scientific progress may feel that it is his or her duty to pursue research and thus eventually establish better therapeutic options, while others may instead feel bound to care for his

or her current patients regardless of medical progress. Furthermore, in such a framework, often there is little to no place for considering the value of the actions including different societal contexts, such as the right of patients to decide whether they want to take part in research or not.

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 questionnaires filled by site personnel explaining their perspective. Sample selection to determine the people who were eligible for participating in the survey were selected based on their fulfillment the following criteria:

- A site personnel working as PI, Sub-I and clinical trial coordinators.
- A site personnel with more than 5 years of experience in clinical research industry.
- A site personnel with more than 2 years of experience in pediatric clinical trials.
- One, who is updated with global and local guidelines on clinical research.
- One, who is updated with global and local guidelines on pediatric trials.
- One, who is willing to voluntarily complete the questionnaire with dedication.
- One, who is willing to share his/her inputs / views / thoughts / knowledge / experience / guidance about issues with recruitment in pediatric trials and measures taken to improve the enrollment rate.

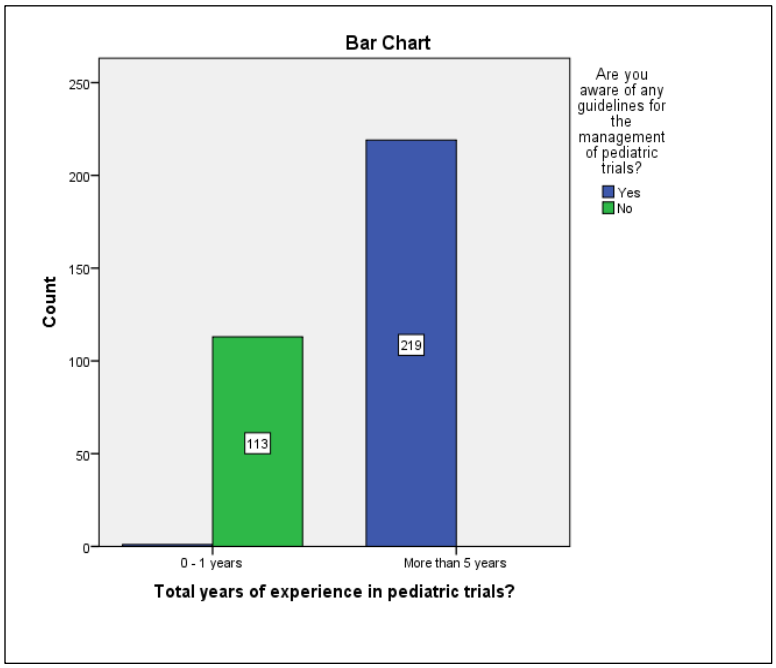
A database was created with the purpose of collecting data from the respondents. The database was designed in order to provide all necessary information on objectives of the project, information on the author, confidentiality statement and consent of participant. The main questionnaire page was sub-divided into various domains namely General, Clinical Research Overview, Regulatory & Ethics, Study Design, Consenting process, Recruitment and Miscellaneous.

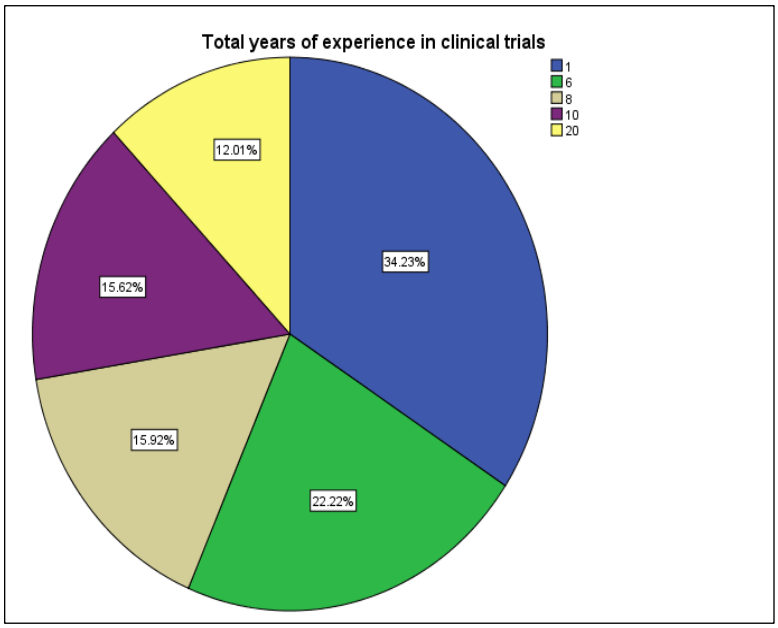
Results

Among the site personnel who participated in the survey, 34.2% had experience of 1 year, while 22.2% had experience of 6 years of participating in clinical trials. Amongst them, 65.8% had experience of more than 5 years in pediatric trials.

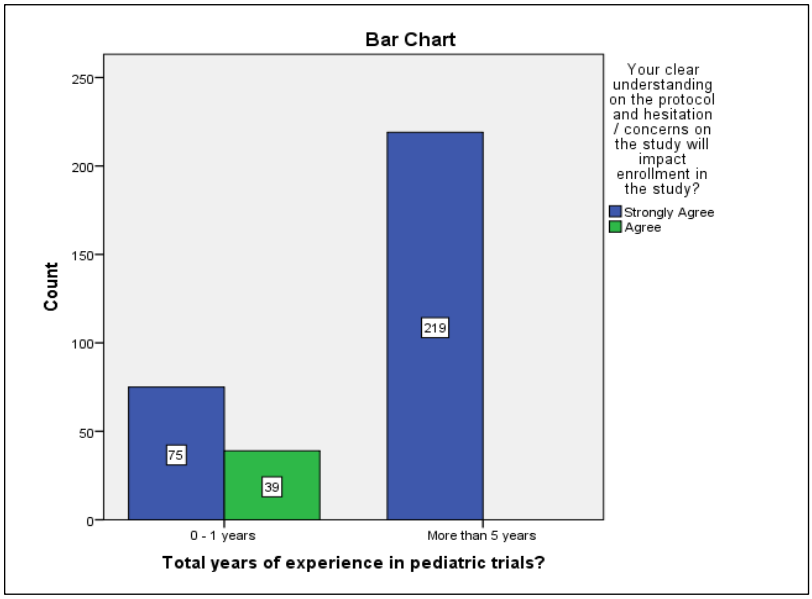
When the participants were asked about their current role / designation in any study ongoing at their site, 68.5% of them stated that they were working as Clinical Research Coordinator (CRC / CTC / CTA), while 31.5% were Principal investigators.

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 participants answered in negative. Those with less than 1 year of experience mostly responded in negative. However, the difference was not found to be significant. The participants were then asked, how important was the conducting of pediatric trials in India. To which 66.1% stated that they believed it to be high. The distribution of responses compared to their experience is presented in the figure below.

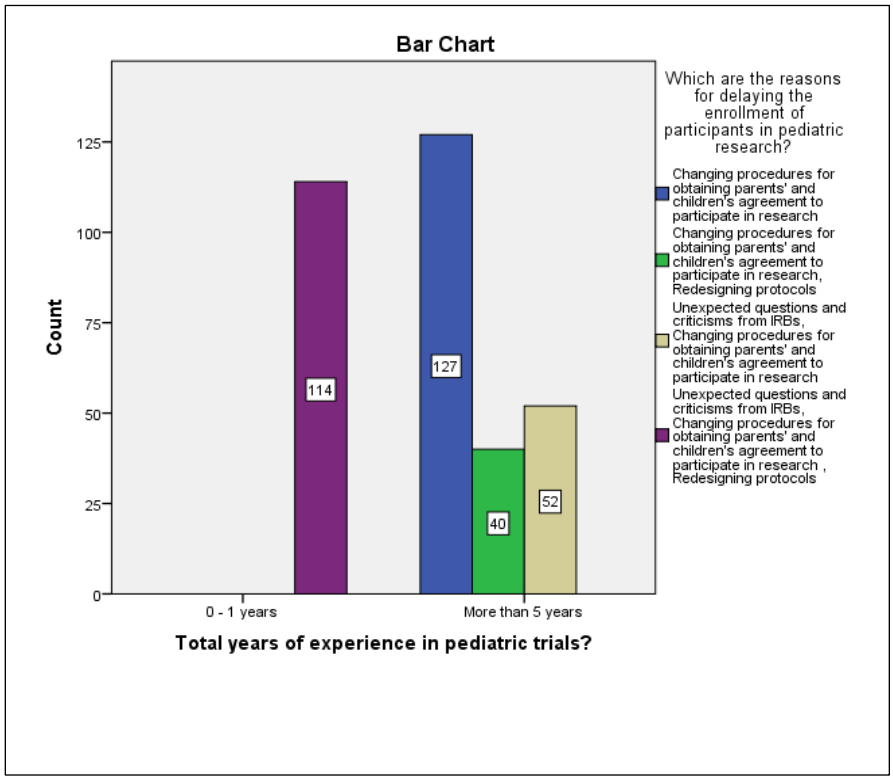


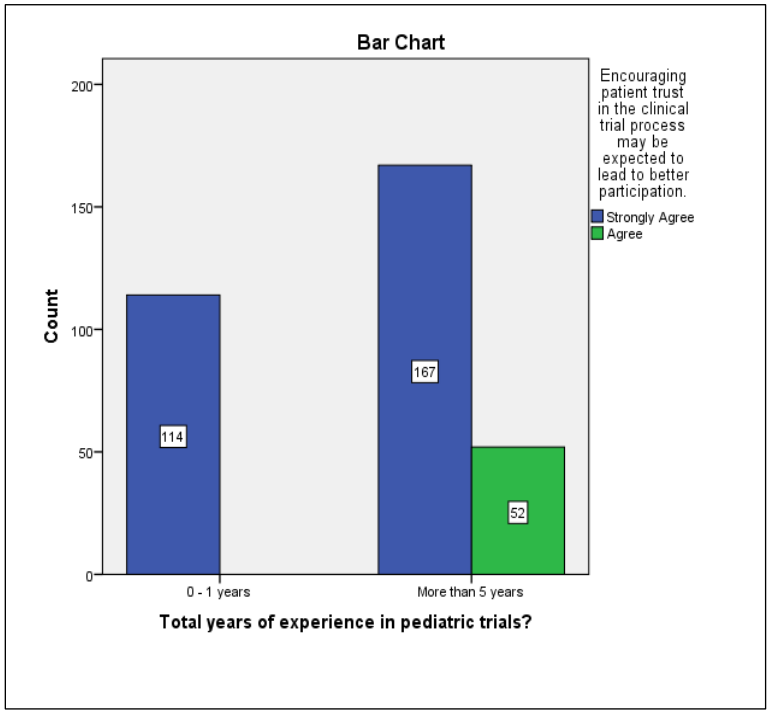


Next, they were asked, if the Investigator/Site Staff doesn't have clear understanding on the protocol and hesitation / concerns on the study, then it will impact enrollment in the study? To this question, 88.3% of the participants stated that they strongly agreed to the notion. No significant variation was observed. The participants were then asked, 'Medical provider should have served as Principal Investigator for how many years to aid with meaningful recruitments in pediatric trials.' To this 38.4% believed 2 to 4 years of experience was needed, while 50.2% believed 5 to 9 years was necessary. Participants with higher experience preferred higher experience for the position.

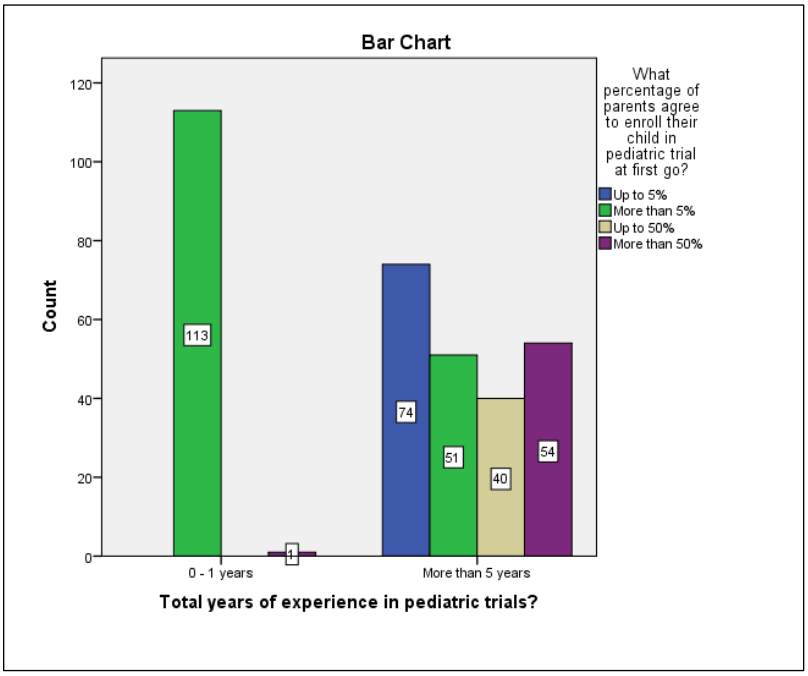


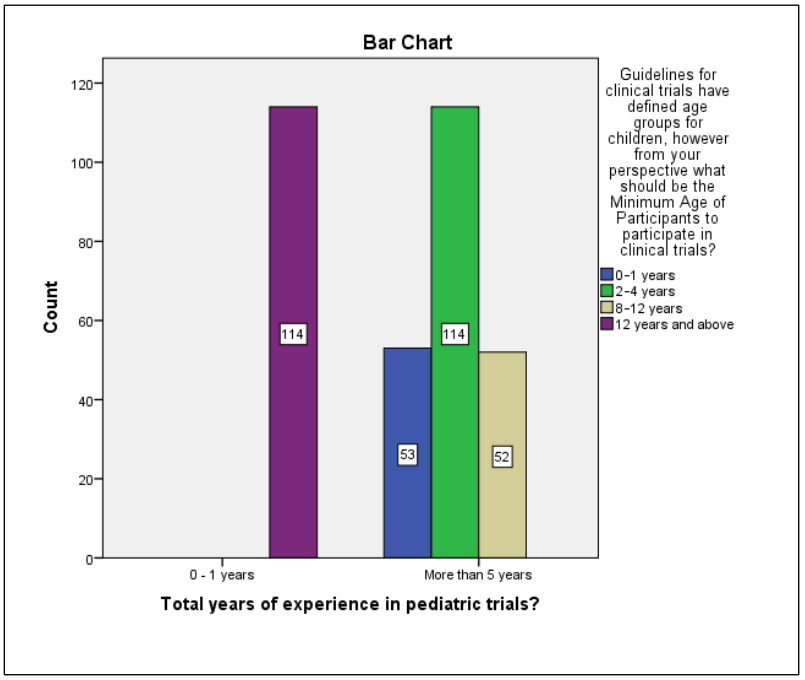
Next, they were asked, what they thought were the reasons for delaying the enrollment in pediatric research. Majority (38.1%) stated that they believed, 'Changing procedures for obtaining parents' and children's agreement to participate in research' was the main reason. While 34.2% stated that unexpected questions and criticisms from IRBs, changing procedures for obtaining parents' and children's agreement to participate in research, redesigning protocols were the main reason. The participants were then asked, 'Encouraging patient trust in the clinical trial process may be expected to lead to better participation'. To this majority of the participants (84.4%) stated that they strongly agreed to the statement, while 15.6% agreed to the statement. No significant variation was observed.



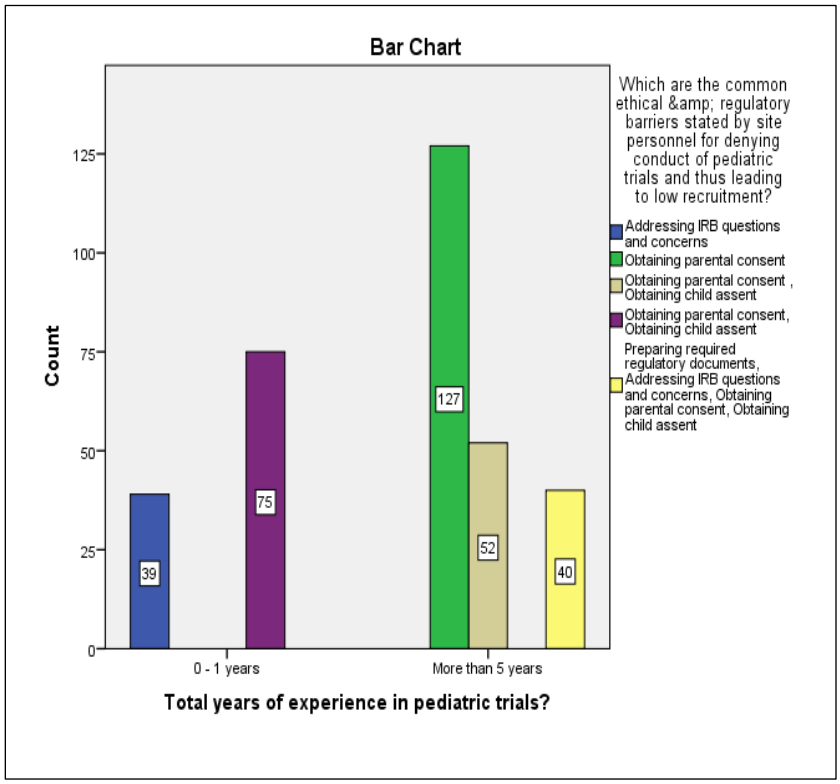


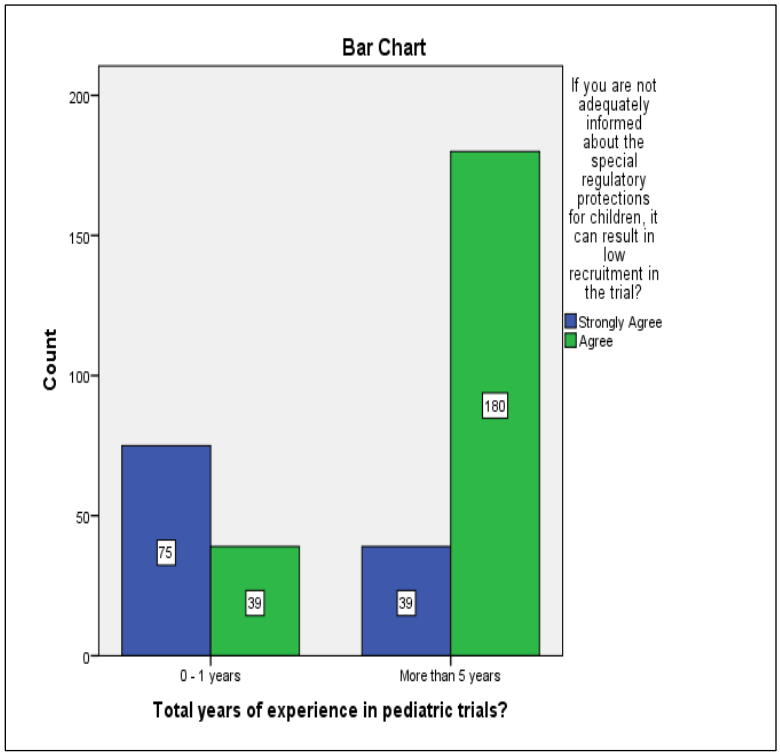
Next, the participants were asked if they thought, limited scientific literacy can in general population be responsible for narrowing the chances of patient enrollment in the trials? 27.3% of the participants agreed to the statement, while 72.7% strongly agreed to it. The participants were then inquired, 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 84.1% of participants strongly agreed and 15.9% participants agreed to the statement. No significant variation was observed. The participants were then asked, 'What percentage of parents agree to enroll their child in pediatric trial at first go?'. To this, 49.2% stated that the rate would be more than 5%. 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% 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. The participants were then asked, according to them how stringent are ICH E2 guidelines for conduct / management of clinical trials in children. To which 46.5% of the participants stated that they were very stringent, while 38.1% stated that they were just adequate.


Bar Chart
What percentage of parents agree to enroll their child in pediatric trial at first go?
Up to 5%
More than 5%
Up to 50%
More than 50%
Count
120
100
80
60
40
20
0
113
1
74
51
40
54
0 - 1 years
More than 5 years
Total years of experience in pediatric trials?


Bar Chart
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?
0-1 years
2-4 years
8-12 years
12 years and above
Count
120
100
80
60
40
20
0
114
53
114
52
0 - 1 years
More than 5 years
Total years of experience in pediatric trials?

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% stated that addressing IRB questions and concerns and obtaining parental consent, was the major barrier. 38.1% stated that the barrier was obtaining parental consent. The distribution of their experience wise responses is presented in figure 98. The responses did show variation among the two different groups, however it was found to be not significant. 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 participants agreed to the statement, while 34.2% strongly agreed to the statement. No significant variation was observed.



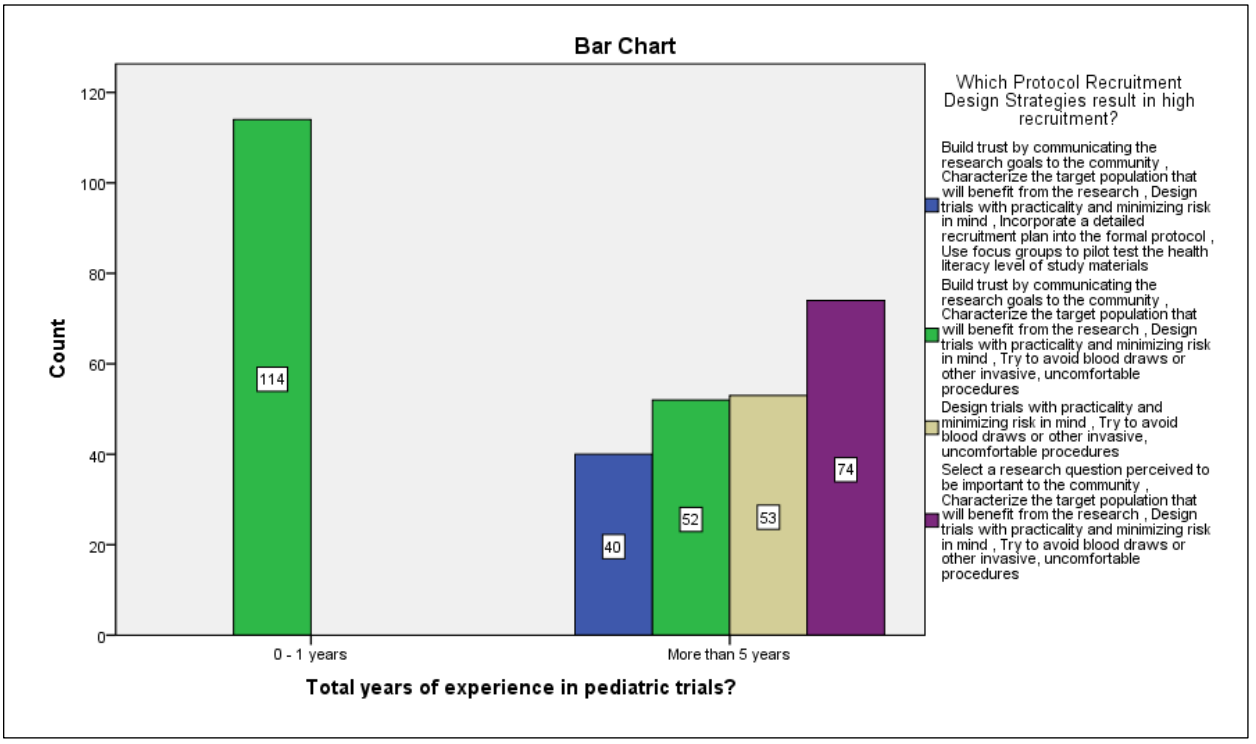


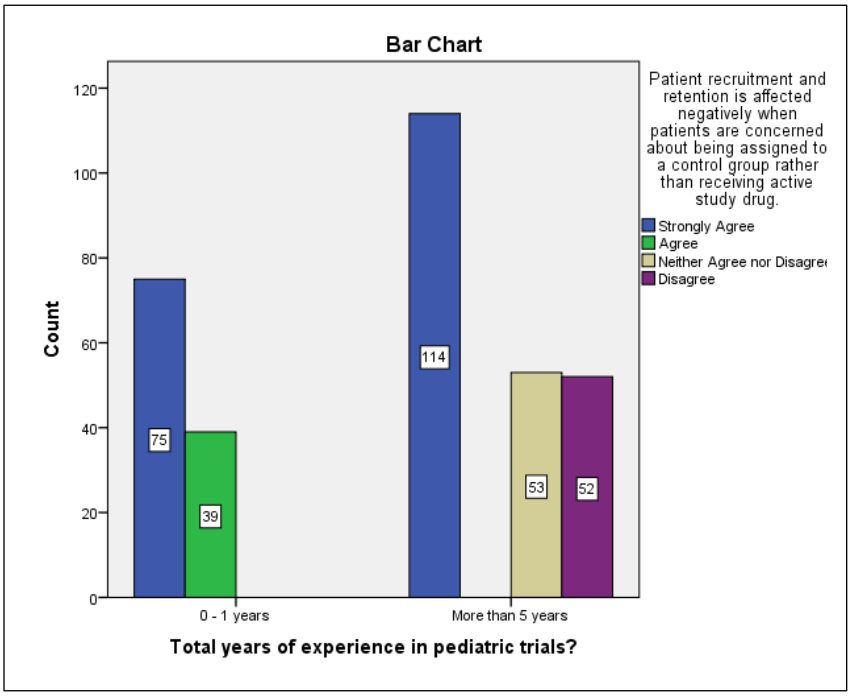
Next, in response to the question, 'The extended time required to gain IRB approval for pediatric studies is one of major reason for low recruitment rate?', majority (65.5%) believed the statement to be false, while 34.5% believed it to be true. Next the participants were asked, if 'Protocol design and strict inclusion/exclusion criteria is known to narrow the recruitment rate in pediatric trials?'. To which 27.6% stated they agreed to the statement, while 44.7% strongly agreed. No significant variation was observed. The participants were then asked, if the duration of clinical trial and number of visits was responsible for lower recruitment. To which 50.2% agreed and another 22.5% stated strongly agree. No significant variation was observed. Next, the participants were asked, if 'The study intervention and indication of the drug have impact on recruitment'. To which, 84.4% stated definitely yes. No significant variation was observed. The participants were then asked, 'Does route of administration and dosage form on drug affect pediatric clinical trial recruitment?' The participants stated 33.9 % to yes, and another 66.1% to definitely yes. Significant difference was observed between the response of the experience wise groups ($\chi 2 = 0.006$, $p = 0.94$).

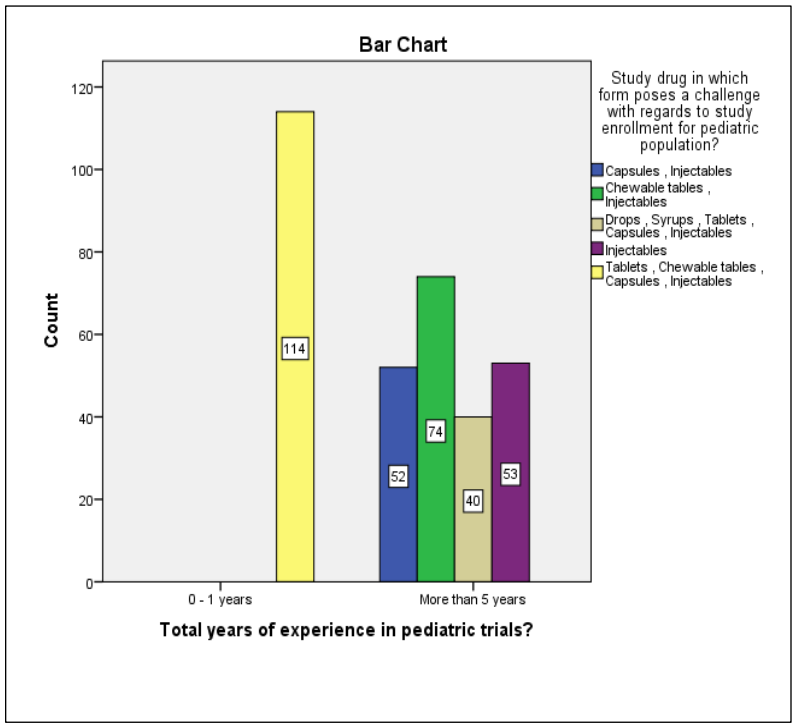
The participants were then inquired, if expanding the number of study centers can help to combat low enrollment? To which 56.8% of the participants strongly agreed. There were no significant difference between the responses of experience wise groups. Next, the participants were asked, 'To what extent does inform consent and assenting process impact pediatric recruitment?'. To this question, 50.2% stated that it was high. No significant variation was observed. Next, the participants were asked, 'What are the factors with respect to ICFs and Assent form that will aid to improve recruitment rate?'. Highest response at 34.2% was attributed to 'Length of the document, Complexity, Information of the study, Language, Others'. The participants were then asked, if the time given by an investigator to explain the study to the patient and provide consent is vital factor influencing enrollment? 84.1% of participants stated 'Yes' to the question. No significant variation was observed. The participants were then asked, which methods can be adopted while Obtaining Informed Consent from Parents / Legal Guardians and Child's Assent that will help in better recruitment and retention of population in the study? To this question, 56.5% of participants stated to provide clear education about the disease or condition being studied, to relay interest in improving care or outcomes for those with the disease or condition, to explain how the parent and child can be part of finding better ways to treat the condition, to explain the randomization process if applicable and the right to withdraw at any time, to create easy to understand print material to keep and use as a reference.

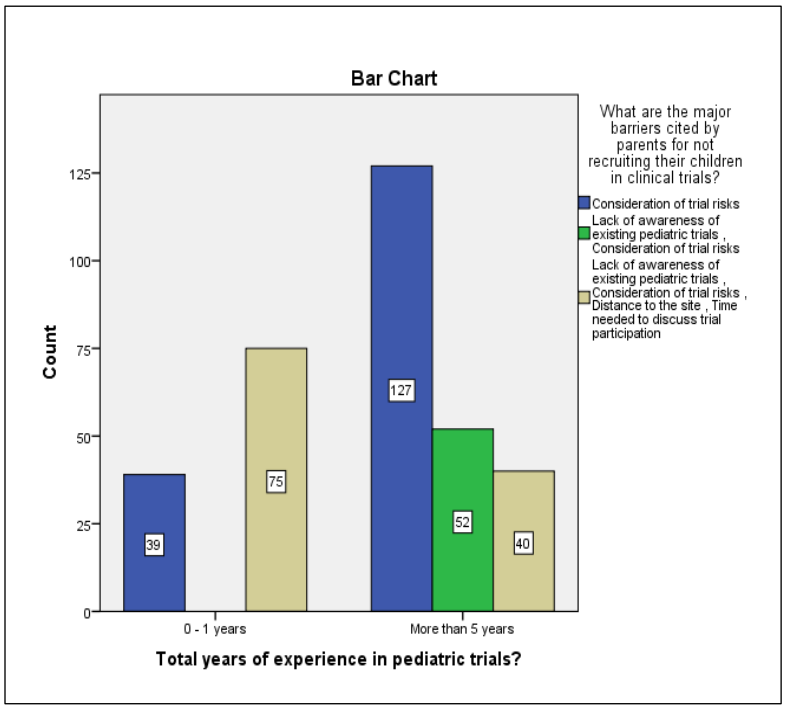
Next, the participants were asked, which option provides highest pool for Pediatric population to enroll in clinical trials? To which 65.8% of participants stated that it was the hospital system. No significant variation was observed. The participants were then asked, how would they describe impact of media on pediatric trials and its enrollment? To this 34.2% stated that the impact was extremely positive. there was no significant difference between the groups.

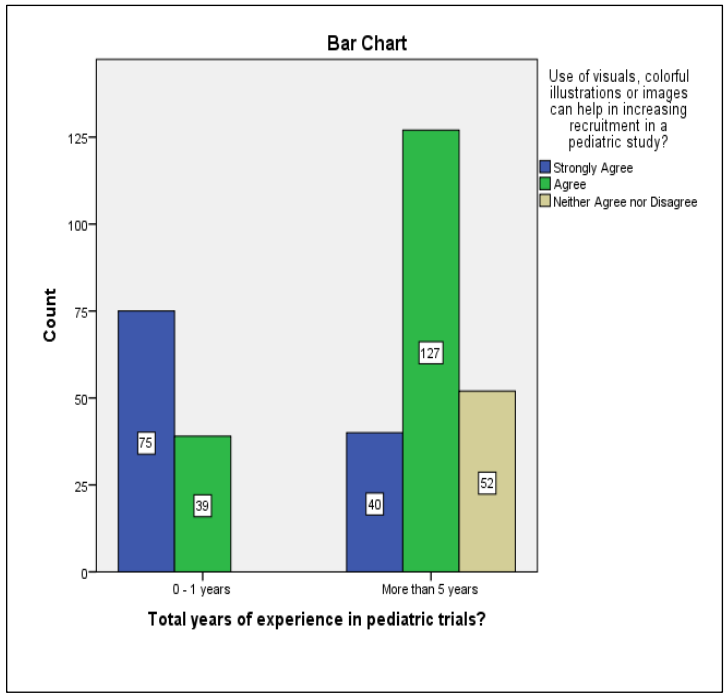
Other Significant results are represented in the figures below:






Bar Chart
Study drug in which form poses a challenge with regards to study enrollment for pediatric population?
Capsules , Injectables
Chewable tables , Injectables
Drops , Syrups , Tablets , Capsules , Injectables
Injectables
Tablets , Chewable tables , Capsules , Injectables
Count
120
100
80
60
40
20
0
114
52
74
40
53
0 - 1 years
More than 5 years
Total years of experience in pediatric trials?


Bar Chart
What are the major barriers cited by parents for not recruiting their children in clinical trials?
Consideration of trial risks
Lack of awareness of existing pediatric trials , Consideration of trial risks
Lack of awareness of existing pediatric trials , Consideration of trial risks , Distance to the site , Time needed to discuss trial participation
Count
125
100
75
50
25
0
39
75
127
52
40
0 - 1 years
More than 5 years
Total years of experience in pediatric trials?



Discussion

Level of awareness about any guidelines for the management of pediatric trialswas not shown to increase with experience. 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 [9]. 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. Health care professionals need to be aware that the decision-making process is only one element of the informed consent process, and it is highly likely that the processes used are reflective of pre-existing decision patterns in families.

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 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. This revealed that the participants 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.

In low- and middle-income countries similar to India, poverty, fear of exploitation, and mistrust represent additional challenges [5]. However, clinical research involving children is essential for advancing child health8. 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 [6]. Pediatric clinical trial participation requires enthusiastic participation. There are several strategies that can be implemented in order to improve enrollment. Most of the site personnel were of the opinion that provide clear education about the disease or condition being studied, to relay interest in improving care or outcomes for those with the disease or condition, to explain how the parent and child can be part of finding better ways to treat the condition, to explain the randomization process if applicable and the right to withdraw at any time, to create easy to understand print material to keep and use as a reference; were the preferred choice for obtaining informed consent from parents / legal guardians and child's assent that will help in better recruitment and retention of population. Doctor-patient relationship was also considered to have a positive impact on enrollment. Considering enrollment through parental consent to be a major factor in clinical trials, a previous study showed the average consent rate for pediatric randomized controlled trials was 82.6%[7].

Conclusion

The present study has successfully documented the responses from the participating stakeholders and has identified the key issues behind low recruitment rate in pediatric clinical trials. As clinical trials involving children become more and more common, it becomes more important to make sure that children understand what they are participating for. People involved in such clinical trials, especially like the ones who were the focus of the present investigation, need to understand that parental decision making is a major part of the entire process of consent. Decision-making during the informed consent process affects the family, not just the child who is the participant. Developing an understanding of decision-making within families prior to the informed consent process will increase the present knowledge of how to improve that process for all families. Better education of the medical community and the general population is much warranted. People need to understand about the rationale and benefits of clinical trials and the potential dangers of using health-care interventions that have not been appropriately studied. Negatively biased media coverage about clinical trials involving children needs to be balanced with public awareness campaigns by sharing of positive case

studies about the societal benefits of clinical trials. Efforts should be undertaken in highlighting the possible harm from unpredicted adverse events because of a lack of pediatric trials.

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