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Research Article

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

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

1. Texila American University.

2. Clinical Research Professional.

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

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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. There has to be extensive exploration on recruitment and retention issues in trials. 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 research objective was achieved by respective questionnaires filled by industry experts from CROs or pharmaceutical companies explaining their perspectives.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.

Keywords*: pediatric trials in India, CROs, Sponsors, recruitment rates.*

Introduction

The need for clinical trials in pediatrics is an international consensus and has become a global public health priority. 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[1].

Ethics in clinical research principally emphasizes on suitable conditions for exposure of clinical trial participants to burden and risk for the benefit of the society. Protocol review, monitoring of subject's safety and well-being, study design, ICF process, etc. has always been in focus and also the same factors have always been overlooked while designing clinical trials. These parameters do affect smooth run of clinical trials as these may alter patients perspective and hence the functioning of the clinical trials. It is equally important to ensure protection of the rights, safety and well-being of human subjects. The dilemma of an investigator becomes even more daunting if the clinical trial involves the participation of children, who are under the legal age of consent and are often beyond the scope of providing informed consent. Despite these ethical issues, one cannot deny the importance of pediatric clinical trials, as clinical trials in children have resulted in significant improvements in their health care.

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[2].

All research in children requires the consent or more accurately, assent of the child. At the most basic level it can be agreed upon that, assent is an affirmative agreement by the child to participate in research. However, in many cases a proxy obtains the consent from the child's parents or guardians. This often puts them in an uncomfortable situation as they are often concerned about unknown or unexpected future side effects and the possibility that the treatment their child receives might later be discovered to be ineffective or even harmful[3].

The both aspects of obtaining assent from participating children and consent from parents pose significant obstacles in conducting pediatric clinical trials. The other obstacles arise from research design and enrolment of participants. 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.

Increasingly more and more countries are beginning to take part in clinical trials and in clinical trials involving children. One of these countries that is becoming more and more relevant due to its vast population and diverse demographic groups is India. India is said to be one of the biggest hub of clinical research, considering various parameters such as large patient pool, diverse population, huge geographical area and cost incurred for the conduct of clinical trials is much less as compared to that of the developed countries, these are what makes India a biggest destination for the conduct of clinical trial and drug development.[5, 4]

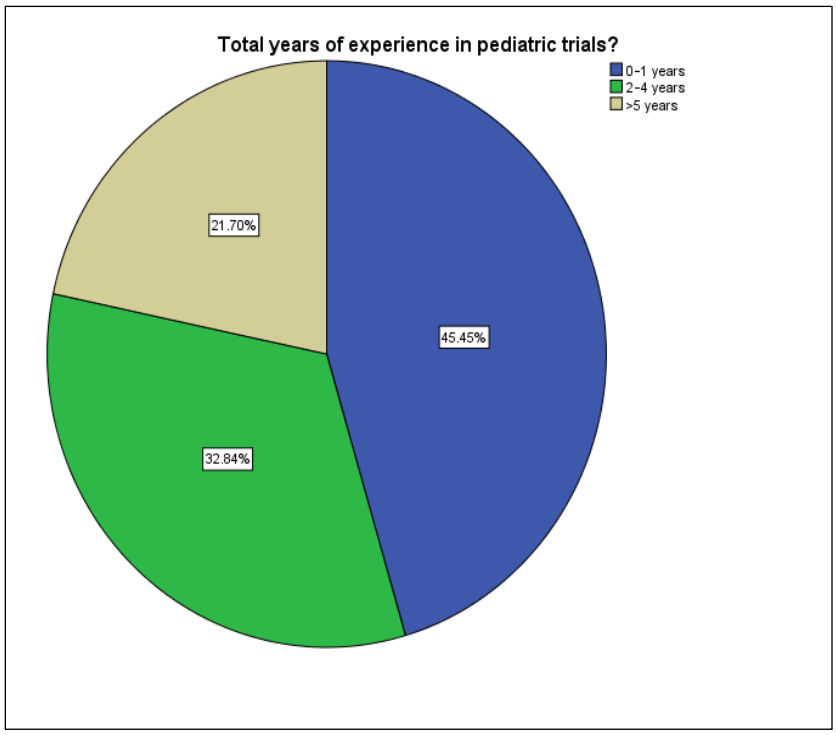
Methodology:

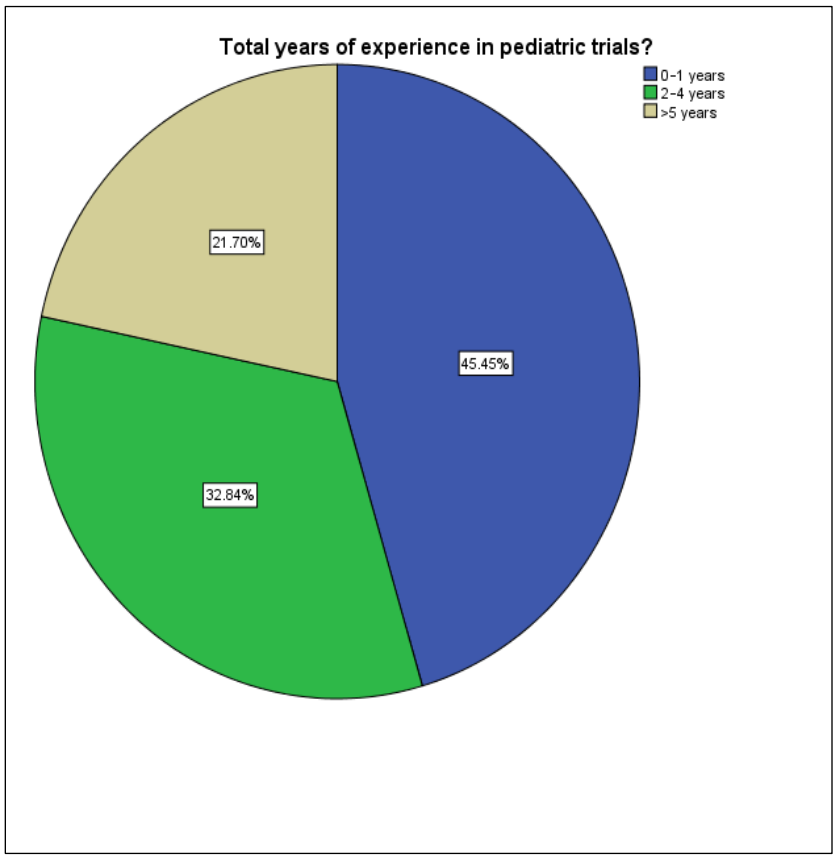
The primary objective of this research project will be to gather data on barriers and facilitators of recruitment in pediatric trials within India. The research study would be conducted through survey from Clinical Research Professionals working with CROs. Data collected from these groups on low recruitment rate in pediatric trials and measures take to improve and maintain the recruitment rate would be analyzed.

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. Post entering into the right portal, the participant was required to answer few basic questions confirming their eligibility. Once the eligibility was confirmed the participants was allowed to answer the questionnaire.

Results

Most of the CROs and sponsors who participated in the study were experienced in the field. 38.71% of the participants had experience between 11 years and 15 years. Only 21.07% had experience of more than 5 years.


Total years of experience in pediatric trials?
0-1 years
2-4 years
>5 years
21.70%
45.45%
32.84%


Total years of experience in pediatric trials?
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21.70%
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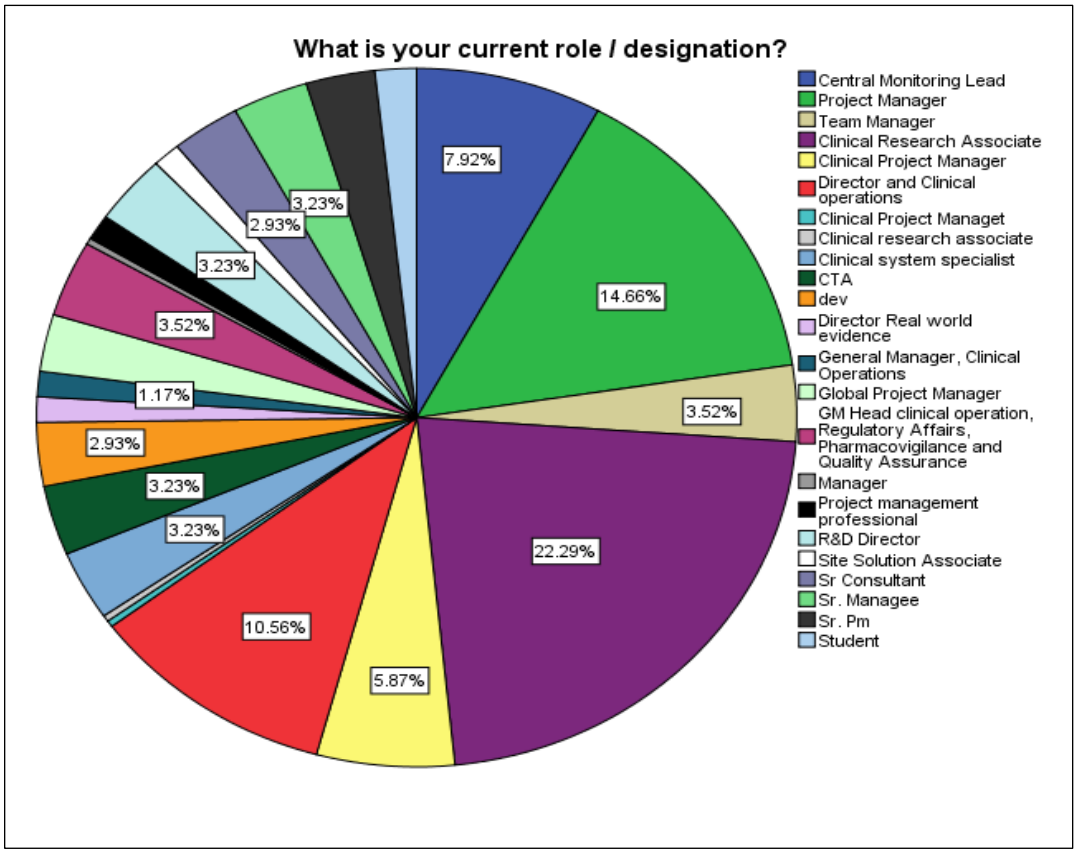
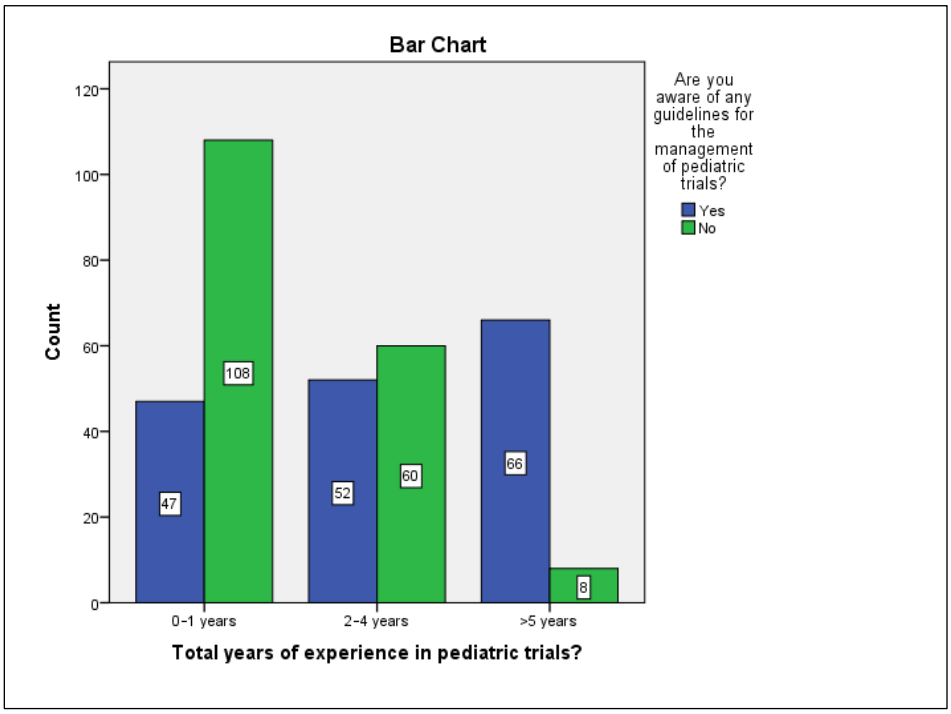
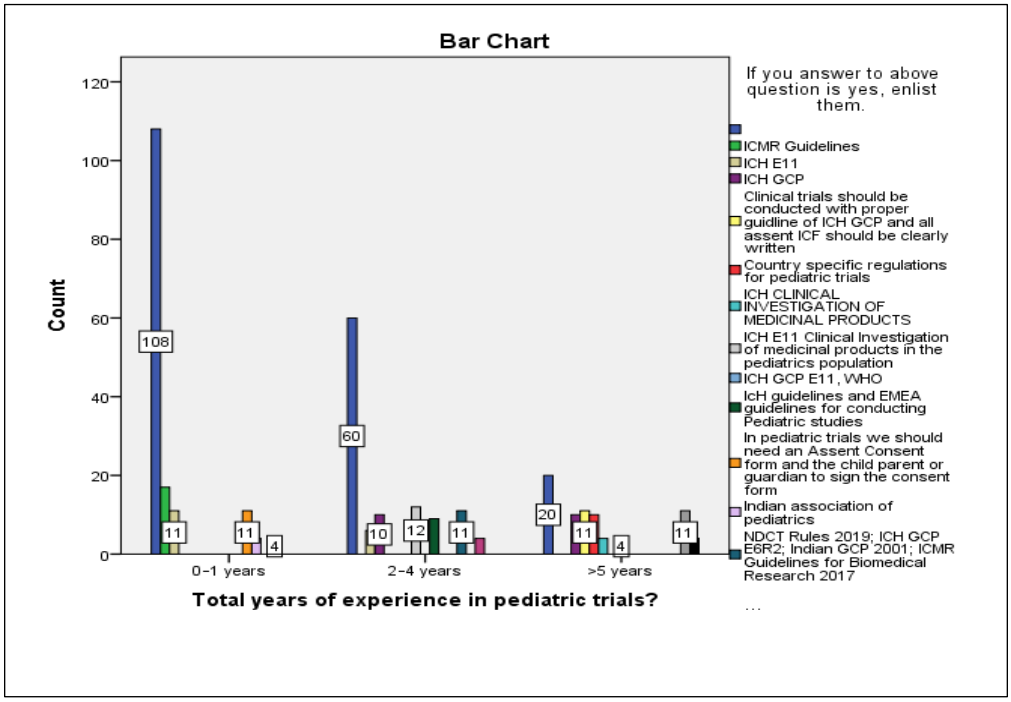


In the questionnaire survey, the responses of the participants were recorded and were compared with the variable of total years of experience in pediatric trials. When the participants were asked if they were aware of any guidelines for the management of pediatric trials 51.6% of the participants answered in negative. No significant variation was observed between the groups with their level of experience. Next, the participants were asked if they could enlist these


Bar Chart
Are you aware of any guidelines for the management of pediatric trials?
Yes
No
Count
120
100
80
60
40
20
0
47
108
52
60
66
8
0-1 years
2-4 years
>5 years
Total years of experience in pediatric trials?


Bar Chart
If you answer to above question is yes, enlist them.
ICMR Guidelines
ICH E11
ICH GCP
Clinical trials should be conducted with proper guidline of ICH GCP and all assent ICF should be clearly written
Country specific regulations for pediatric trials
ICH CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS
ICH E11 Clinical Investigation of medicinal products in the pediatrics population
ICH GCP E11, WHO
IcH guidelines and EMEA guidelines for conducting Pediatric studies
In pediatric trials we should need an Assent Consent form and the child parent or guardian to sign the consent form
Indian association of pediatrics
NDCT Rules 2019; ICH GCP E6R2; Indian GCP 2001; ICMR Guidelines for Biomedical Research 2017
...
Count
120
100
80
60
40
20
0
108
11
11
4
60
10
12
11
20
11
4
11
0-1 years
2-4 years
>5 years
Total years of experience in pediatric trials?

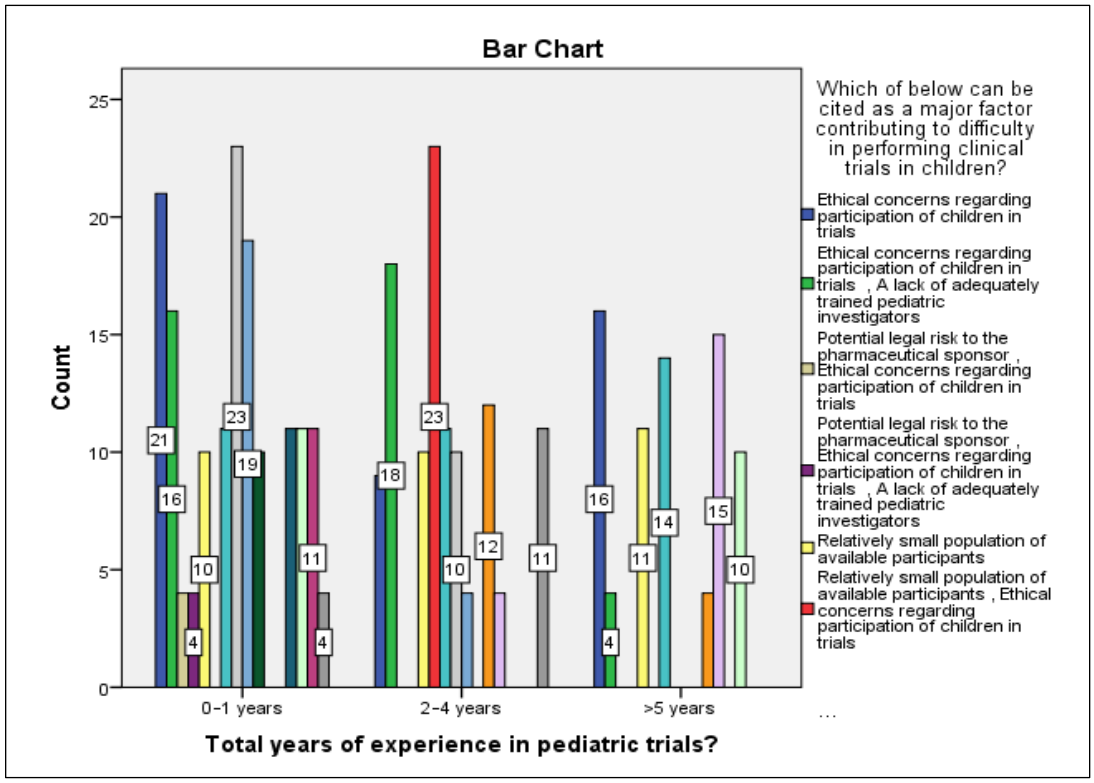
The participants were then asked, how important was the conducting of pediatric trials in India. To which 47.5% stated that they believed it to be high. No significant difference with respect to experience on the responses was found. Next, they were asked, if the Investigator/Site Staff doesn't have clear understanding on the protocol and hesitation / concerns on the study, then it will impact enrollment in the study? To this question, 88% 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 question no clear consensus was reached. 36.4% believed 2 to 4 years of experience was needed, while 33.4% believed 5 to 9 years was necessary. No significant variation was observed. Next, they were asked, what they thought were the reasons for delaying the enrollment in pediatric research. Majority (34.0%) stated that they believed, 'Changing procedures for obtaining parents' and children's agreement to participate in research' was 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 (68.3%) stated that they strongly agreed to the statement, while 31.7% 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? 49.3% of the participants agreed to the statement, while 28.7% strongly agreed to it. No significant variation was observed.

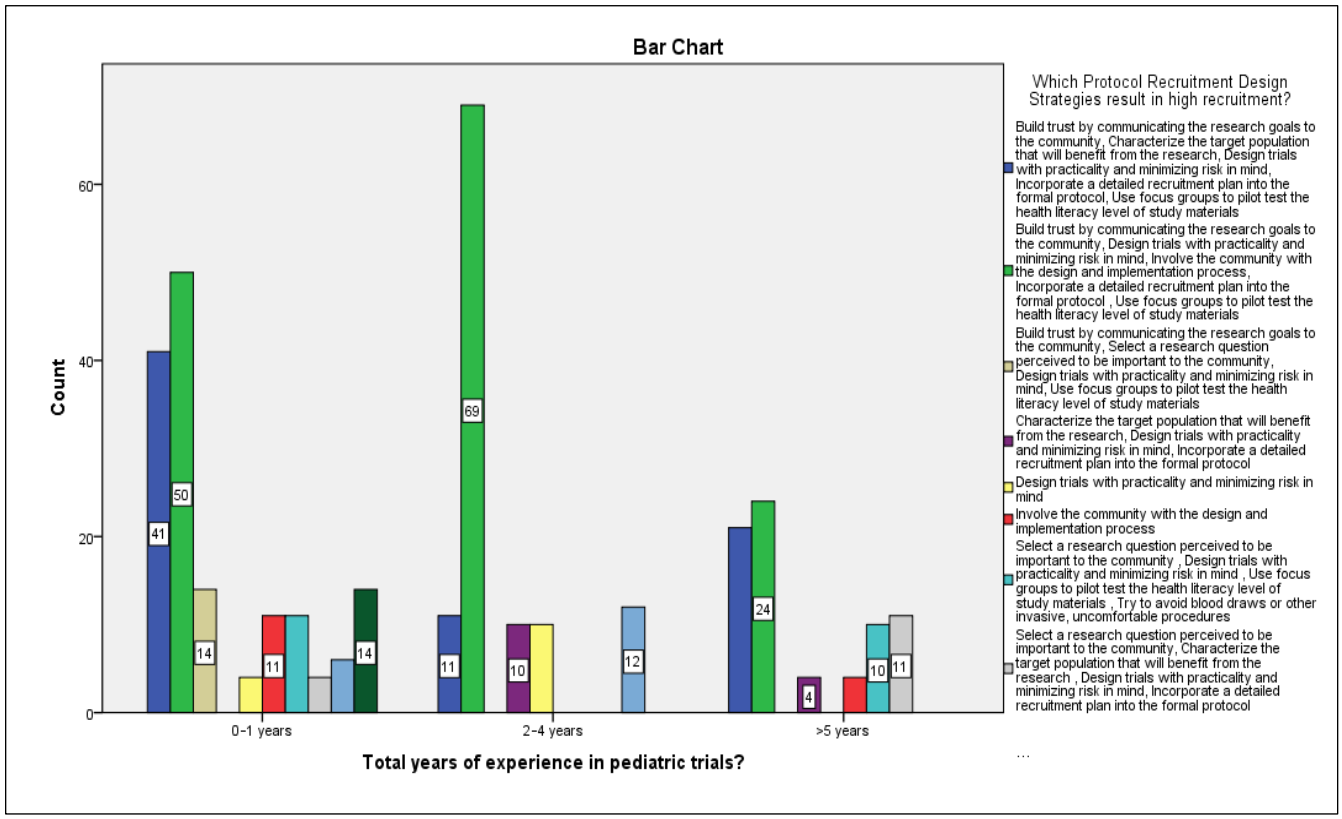
Next, the following question was posed to the participants, 'Guidelines for clinical trials have defined age groups for children, however from your perspective what should be the Minimum Age of Participants to participate in clinical trials?'. To this, 25.8% stated that minimum age should be between 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. The participants were then asked, if the participants thought safety concerns and adverse effects of the study drug impacts enrollment. 49.6% of participants agreed to the statement, while another 42.5% stated that they strongly agreed. The participants were then asked, if the participants thought safety concerns and adverse effects of the study drug impacts enrollment. 49.6% of participants agreed to the statement, while another 42.5% stated that they strongly agreed. Next, 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, 27.6% stated that addressing IRB questions and concerns and

obtaining parental consent, was the major barrier. 20.8% 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?', 53.7% of the participants agreed to the statement, while 29.9% 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 (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 53.4% stated they agreed to the statement, while 27.6% 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 55.4% stated yes and another 27.9% stated definitely yes. 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, 52.5% agreed and 34% strongly agreed. 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 51.6 % to yes, and another 30.5% to definitely yes. The experience wise breakdown is presented in figure 51. There were no significant difference between the responses of experience wise groups.

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 25.2% was attributed to 'Information of the study, Language'. 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? 90% 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, 36.7% 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.


Bar Chart
Count
Total years of experience in pediatric trials?
0-1 years
2-4 years
>5 years
Which of below can be cited as a major factor contributing to difficulty in performing clinical trials in children?
Ethical concerns regarding participation of children in trials
Ethical concerns regarding participation of children in trials , A lack of adequately trained pediatric investigators
Potential legal risk to the pharmaceutical sponsor , Ethical concerns regarding participation of children in trials
Potential legal risk to the pharmaceutical sponsor , Ethical concerns regarding participation of children in trials , A lack of adequately trained pediatric investigators
Relatively small population of available participants
Relatively small population of available participants , Ethical concerns regarding participation of children in trials


Bar Chart
Count
Total years of experience in pediatric trials?
0-1 years
2-4 years
>5 years
Which Protocol Recruitment Design Strategies result in high recruitment?
Build trust by communicating the research goals to the community, Characterize the target population that will benefit from the research, Design trials with practicality and minimizing risk in mind, Incorporate a detailed recruitment plan into the formal protocol, Use focus groups to pilot test the health literacy level of study materials
Build trust by communicating the research goals to the community, Design trials with practicality and minimizing risk in mind, Involve the community with the design and implementation process, Incorporate a detailed recruitment plan into the formal protocol , Use focus groups to pilot test the health literacy level of study materials
Build trust by communicating the research goals to the community, Select a research question perceived to be important to the community, Design trials with practicality and minimizing risk in mind, Use focus groups to pilot test the health literacy level of study materials
Characterize the target population that will benefit from the research, Design trials with practicality and minimizing risk in mind, Incorporate a detailed recruitment plan into the formal protocol
Design trials with practicality and minimizing risk in mind
Involve the community with the design and implementation process
Select a research question perceived to be important to the community , Design trials with practicality and minimizing risk in mind , Use focus groups to pilot test the health literacy level of study materials , Try to avoid blood draws or other invasive, uncomfortable procedures
Select a research question perceived to be important to the community, Characterize the target population that will benefit from the research , Design trials with practicality and minimizing risk in mind, Incorporate a detailed recruitment plan into the formal protocol

44.3% of the participants agreed to when they were asked ‘recruiter flexibility and building rapport with patients known to have major impact on willingness of parents to allow their child to get enrolled in trials?’. 41.9% of participants stated they believed in

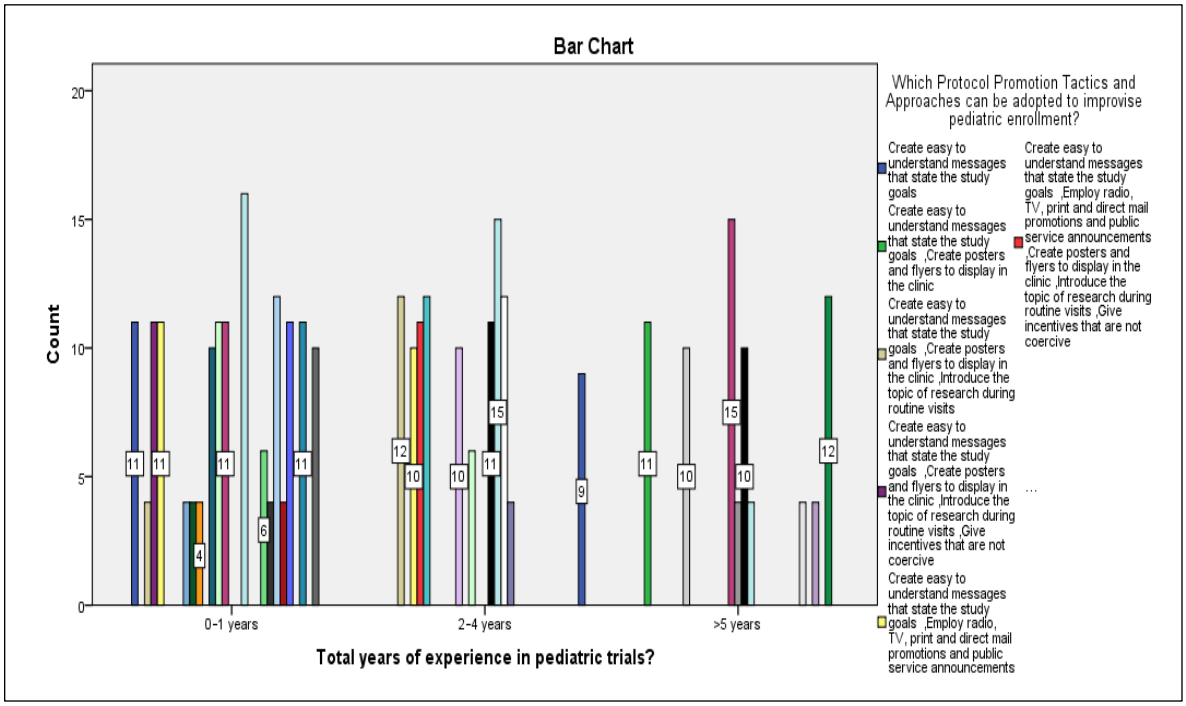
- building trust by communicating the research goals to the community,

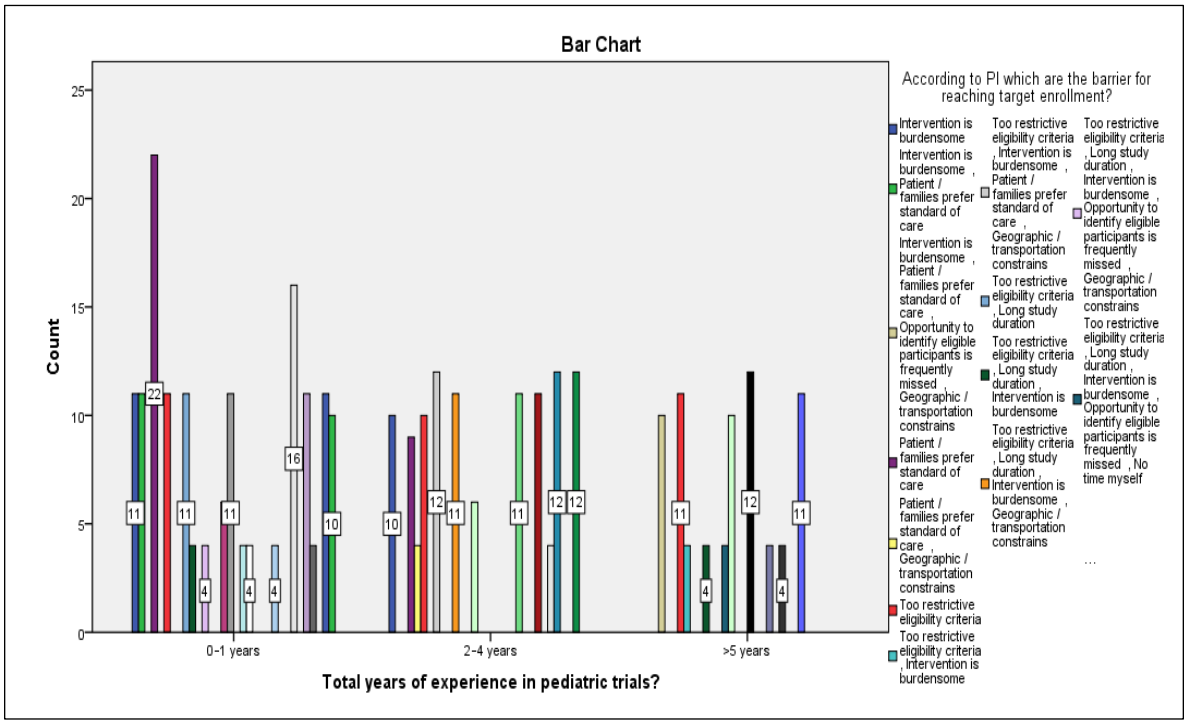
- design trials with practicality and minimizing risk in mind,

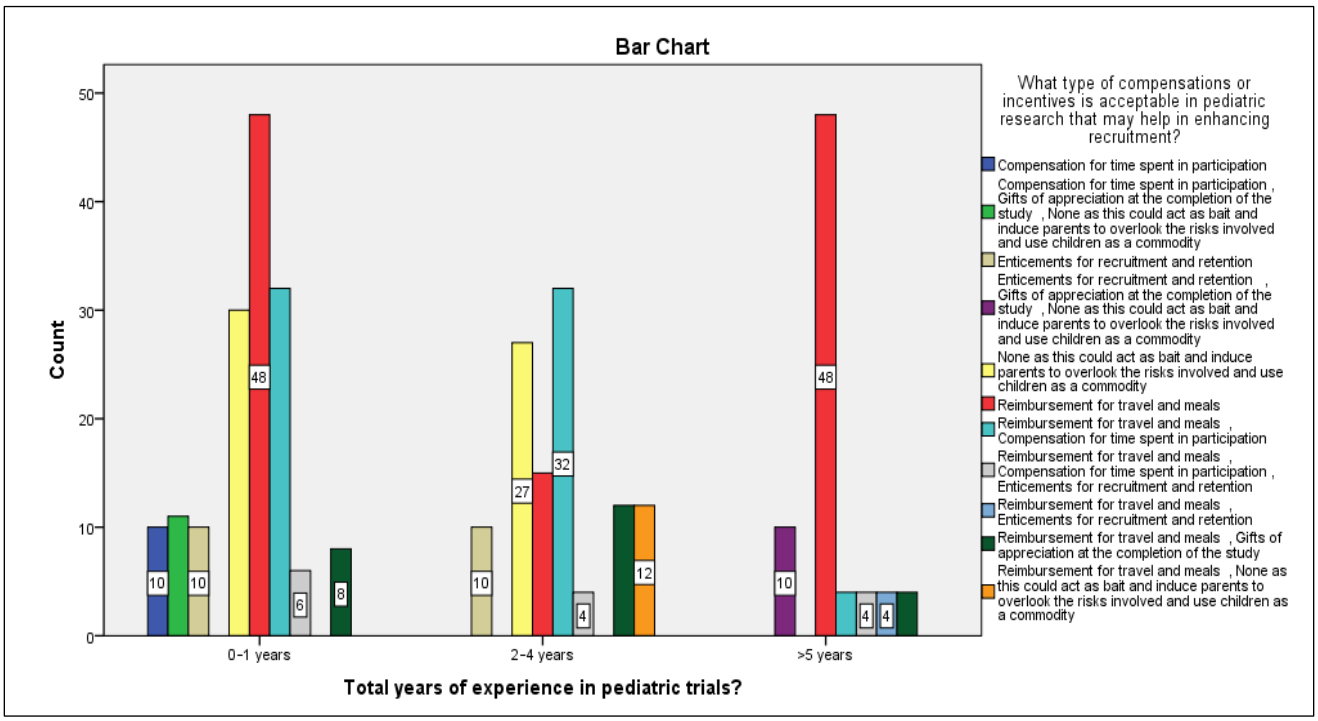
- involve the community with the design and implementation process,

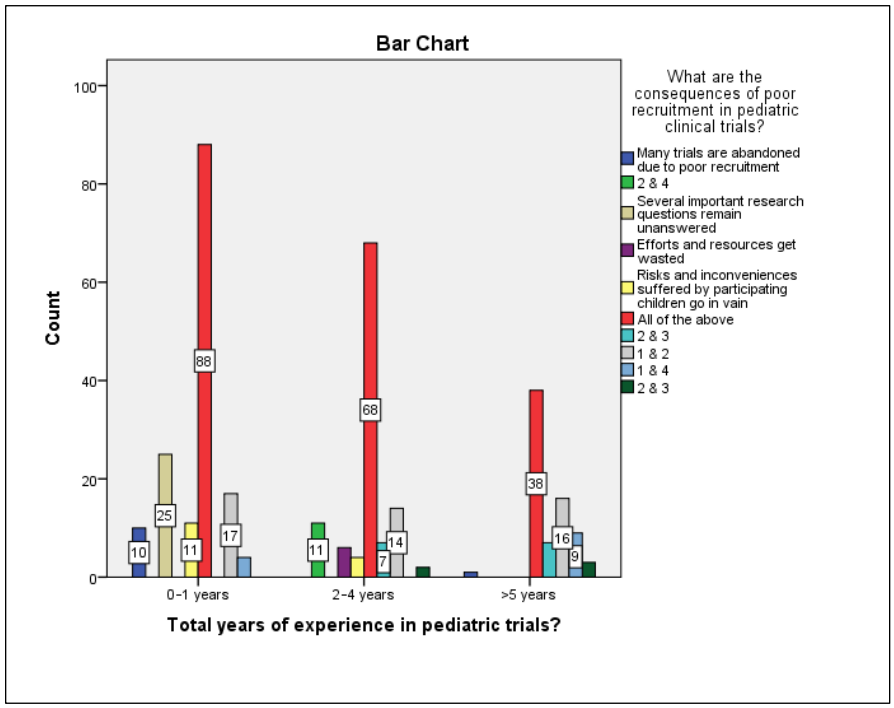
- incorporate a detailed recruitment plan into the formal protocol,

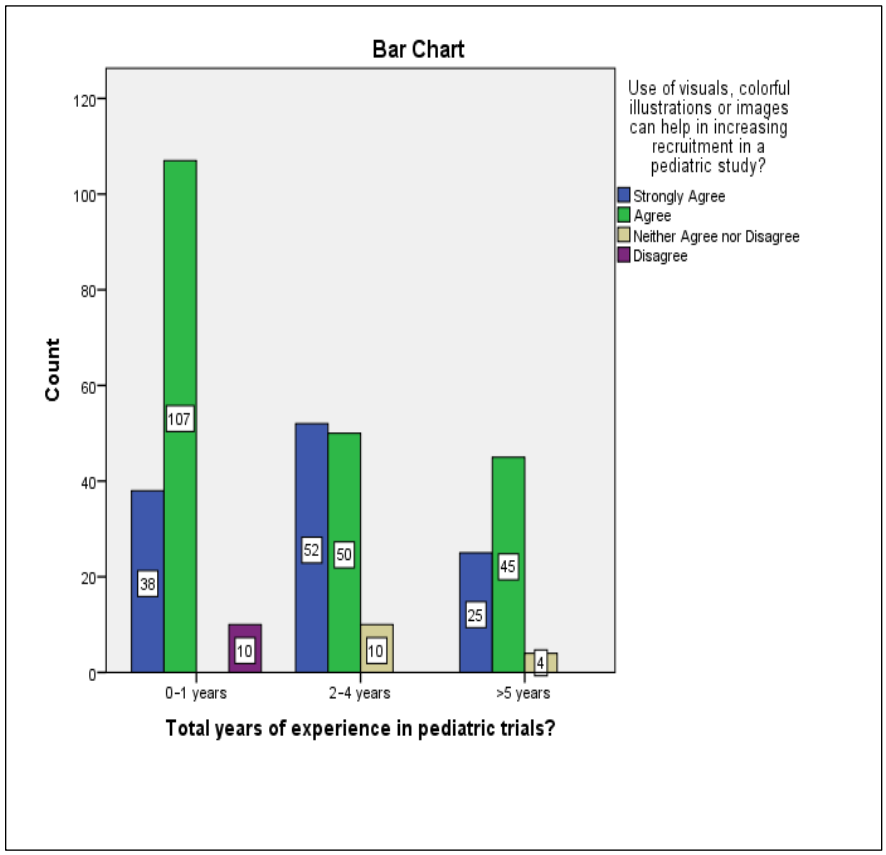
- use focus groups to pilot test the health literacy level of study materials; when they were asked the question ‘Which Protocol Recruitment Design Strategies result in high recruitment?’




Bar Chart
Count
Total years of experience in pediatric trials?
0-1 years
2-4 years
>5 years
According to PI which are the barrier for reaching target enrollment?
Intervention is burdensome
Intervention is burdensome , Patient / families prefer standard of care
Intervention is burdensome , Patient / families prefer standard of care , Opportunity to identify eligible participants is frequently missed , Geographic / transportation constrains
Patient / families prefer standard of care
Patient / families prefer standard of care , Geographic / transportation constrains
Too restrictive eligibility criteria
Too restrictive eligibility criteria , Intervention is burdensome
Too restrictive eligibility criteria , Intervention is burdensome , Patient / families prefer standard of care , Geographic / transportation constrains
Too restrictive eligibility criteria , Long study duration
Too restrictive eligibility criteria , Long study duration , Intervention is burdensome
Too restrictive eligibility criteria , Long study duration , Intervention is burdensome , Geographic / transportation constrains
Too restrictive eligibility criteria , Long study duration , Intervention is burdensome , Opportunity to identify eligible participants is frequently missed , Geographic / transportation constrains
Too restrictive eligibility criteria , Long study duration , Intervention is burdensome , Opportunity to identify eligible participants is frequently missed , No time myself
...


Bar Chart
Count
Total years of experience in pediatric trials?
0-1 years
2-4 years
>5 years
What type of compensations or incentives is acceptable in pediatric research that may help in enhancing recruitment?
Compensation for time spent in participation
Compensation for time spent in participation , Gifts of appreciation at the completion of the study , None as this could act as bait and induce parents to overlook the risks involved and use children as a commodity
Enticements for recruitment and retention
Enticements for recruitment and retention , Gifts of appreciation at the completion of the study , None as this could act as bait and induce parents to overlook the risks involved and use children as a commodity
None as this could act as bait and induce parents to overlook the risks involved and use children as a commodity
Reimbursement for travel and meals
Reimbursement for travel and meals , Compensation for time spent in participation
Reimbursement for travel and meals , Compensation for time spent in participation , Enticements for recruitment and retention
Reimbursement for travel and meals , Enticements for recruitment and retention
Reimbursement for travel and meals , Gifts of appreciation at the completion of the study
Reimbursement for travel and meals , None as this could act as bait and induce parents to overlook the risks involved and use children as a commodity


Bar Chart
What are the consequences of poor recruitment in pediatric clinical trials?
Many trials are abandoned due to poor recruitment
2 & 4
Several important research questions remain unanswered
Efforts and resources get wasted
Risks and inconveniences suffered by participating children go in vain
All of the above
2 & 3
1 & 2
1 & 4
2 & 3
Count
0-1 years
2-4 years
>5 years
Total years of experience in pediatric trials?


Bar Chart
Use of visuals, colorful illustrations or images can help in increasing recruitment in a pediatric study?
Strongly Agree
Agree
Neither Agree nor Disagree
Disagree
Count
0-1 years
2-4 years
>5 years
Total years of experience in pediatric trials?

When the participants were asked, 'What are the possible reasons cited by parents / children for not enrolling in pediatrics trials?'. To this 51% stated the main reason to be, children may also have less availability because they are avoiding school absences and working parents may have trouble taking time off from work. Next, the participants were asked, 'What are the chances of child's primary physician referring their pediatric patients to a clinical trial?'. To this 46.6% stated that the chance was moderate. In response to the question, 'Study drug in which form poses a challenge with regards to study enrollment for pediatric population?', 31.7% stated that it were injectable drugs. 54.8% of the participants stated they agreed to the statement, 'Close contact and regular follow ups with families can be adopted by study coordinators to encourage retention of the child in the trial'. 51.9% agreed to the statement, 'Patient recruitment and retention is affected negatively when patients are concerned about being assigned to a control group rather than receiving active study drug'

6. Discussion:

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 administration of harmful treatments, while withholding beneficial treatments.

The presented work sheds new light on understanding the perspective, strategies, issues from Clinical Research Professionals working with CROs / Sponsors. The primary objective of the present thesis was to understand the reasons for low recruitment in pediatric trials in India and drawing strategies for improving its rate. This was done while investigating additional objectives, which aimed to understand issues for recruitment in pediatric trials and strategies adopted by project managers, project leads and CRAs within CRO and Sponsor organizations.

Many ineffective and even harmful interventions are used in children before they have been appropriately assessed in randomized trials50. Majority of the research 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. 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. 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, the group of CROs and sponsors were in 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. One major part of the presented survey focused on figuring out the factors that limited the number of clinical trials being conducted in India.

When the participants were asked if safety concerns and adverse effects of the study drug impact the enrollment rate, majority of the CROs and sponsors agreed to the statement. Another factor behind low recruitment can stem from common ethical and regulatory barriers that have been put in place to provide oversight. To this, obtaining parental consent appeared as a major cause of low recruitment according to the professionals.

Extended time required to gain IRB approval for pediatric studies was also recognized to lower recruitment rates by almost half of the CROs, while majority of the site personnel did not agree to it. The participants were given other options to behind low enrollment rate. For instance, when CROs were asked if they agreed that, protocol design and strict inclusion/exclusion criteria was known to narrow the recruitment rate in pediatric trials; majority of the respondents agreed to the statement. Among other factors that were considered to be limiting the number of participants were, the duration of clinical trial and number of visits required, study intervention and indication of the drug, route of administration and dosage form on drug. All these factors are important determinants of the success of clinical trials.

In low- and middle-income countries similar to India, poverty, fear of exploitation, and mistrust represent additional challenges6. However, clinical research involving children is essential for advancing child health7. Without sound drug studies in children, children may not benefit from and may even be harmed by drugs with an indication for use in adults8.

7. Conclusion:

The face of clinical research changes rapidly and new ethical dilemmas will arise continually to challenge all clinical research professionals and regulatory agencies this would also change the perception of individual. Funding in developing countries for research is also the subject of attention. Clinical trials in

India also raise a concern whether the trial is relevant to the treatment of Indian population or it is just to provide a data to developed countries. Sometimes, India does not enjoy benefits of new treatment since the treatment is too expensive that Indian population may not afford or it might not be available in Indian market. Individuals who are unaware of all the necessary parameters and who already have a negative perception about the clinical trials will not be happy with any kind of trials and facilities given.

The in depth survey undertaken in this study has clearly shown that experience was not a major controlling variable in case of strategies adopted by project managers, project leads and CRAs within CRO and Sponsor organizations. The present study has successfully documented the responses from all participating stake holders and has identified the key issues behind low recruitment rate in pediatric clinical trials. The incorporation of ideas presented by personnel involved in research can further the cause of clinical trials. Findings from the study can help to improve enrollment in pediatric clinical trials. The development of a national or international infrastructure for clinical research, and the provision of infrastructure support to assist with the recruitment and co-ordination of trials in individual centers, supported and funded by government and national research agencies will improve the conduct of pediatric trials. Children might be left behind if government, researchers, and industry conclude that it’s just too hard, too complicated, too risky, and too expensive.

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