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Research Article

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

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Abstract

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. Government, industry, funding agencies, and clinicians are responsible for research priorities being adult-focused due to the increased burden of disease in adults, coupled with financial and marketing considerations. Clinical trials in children are more challenging than those in adults. 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. This study provides a clear picture about the awareness in Indian population and their knowledge and perception about clinical research. The responses from participants indirectly provides few suggestions where we can improve our standard, and can minimize ethical challenges.

Keywords: *Paediatric clinical trials, Parent's perspective, ethical challenges, awareness*.

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 to permit the research to proceed. 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, particularly infants, respond differently to drugs and other medical treatments than adults. There are multiple instances of drugs that, while behaving safely in adults, have serious and even fatal side effects in children[1]. Therefore, trials involving children often require longer follow-ups than 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.

All research in children requires the consent or assent of the child. However, there are several questions surrounding such assent. How is this assent defined? At what age is a child capable of assent? When should it be sought? Answers to these questions are often vague and vary from investigator to investigator. At the most basic level it can be agreed upon that, assent is an affirmative agreement by the child to participate in research. Apart from the assent from the participating child, another important factor in pediatric clinical trials is the consent of the parent. The balance of perceived benefits and potential barriers or risks of participation, and the importance of the study plays a major role in influencing the parents' willingness to participate [3,4,5]. Potential benefits in the eyes of the parents often include the opportunity to access new treatments, better care being given to their child, gaining greater access to health-care professionals. It also gives them new health information through meeting others in similar circumstances, gaining hope when no other effective treatments are available, and the satisfaction of knowing they are helping other children in the future. Potential barriers to parental consent often includes protective parental instincts which often centers around the fear of their child being treated as a "Guinea pig" along with anxiety about the unknown factors inherent in research, and concern that researchers' priorities might not be in the child's best interest. Parents often consider risks involved in such clinical studies which include known and unknown side

effects, the chance that their child might be randomized to an ineffective treatment, and the inconvenience associated with participation. Such inconvenience often involves extra blood tests and time demands encompassing additional clinic visits [6,7,8].

Involving children in matters of medical investigation is not a modern development. Edward Jenner, the father of immunology, used children in his work on smallpox in the late 1700s. He even included his own infant son in his trials of early vaccination. Similarly, Joseph Lister, a pioneer in preventive medicine used children in his work on wound infections. Louis Pasteur first tried his vaccine for rabies on a child who had been bitten by a rabid dog. These initial forays into pediatric clinical trials had their fair share of ethical issues. Even more recently, clinical trials involving children have failed to adequately protect the participants. In the early 20th century, children at the Hebrew Orphan Asylum were fed diets known to induce scurvy and rickets so that these diseases might be better understood[9]. A time when the special population including children were absolutely excluded from clinical trials and the only equivalent were extrapolation of trial data from adult studies and appropriation of doses in pediatric prescription based on those. However, the evolution of regulations and scientific advancement made way for clinical trials involving children and long and complex documents for informed consent that could take almost 60 minutes to read for a parent who wishes to enroll his/her child in a clinical study[10]. Many children are not well equipped to partake in decisions about their participation in research. Even those children who can participate in such decisions, are often unable to fully understand the risks and benefits. Parents, physicians, and scientists all have an obligation to protect children from any negative effects clinical trials may have research but they may also fervently hope to discover new treatments or cures for childhood illnesses. The tension between these two goals – protection and progress – is inevitable.

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[11]. Many investigations have shown that such inclusions provide benefit to all participants of the clinical trial, which include children. This is referred to as the Hawthorn effect[12,13]. 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[14].

Despite the potential benefits of participating in clinical trials, children may also be 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 participation15.

Methodology

The primary objective of this research project will be to gather data from the parents or guardians, an overview on their take on clinical trials and ease of allowing their child to participate in these trials. The research study would be conducted through survey of parents of the children. Sample selection to determine the people who were eligible for participating in the survey were selected based on their fulfillment the following criteria:

One who is willing to participate is a parent / legal guardian.

A parent having children up to / below 12 years of age.

One, who is willing to voluntarily complete the questionnaire with dedication.

One, who is literate and able to understand and interpret the questionnaire.

A database was created with the purpose of collecting data from the respondents. The database was designed to provide all necessary information on objectives of the project, information on the author, confidentiality statement and participant consent.

Results

The first section of the survey aimed to detail the demographics of the participants. The collected data provides an overall idea about the participants, their educational qualification and further details, which were essential in understanding their choices.

The total number of participants in the survey was 431, of which 122 (28.3%) were males and 309 (71.7%) were females. Based on age, 49.4% of participants were aged between 35 to 45 years, and 41.5% were

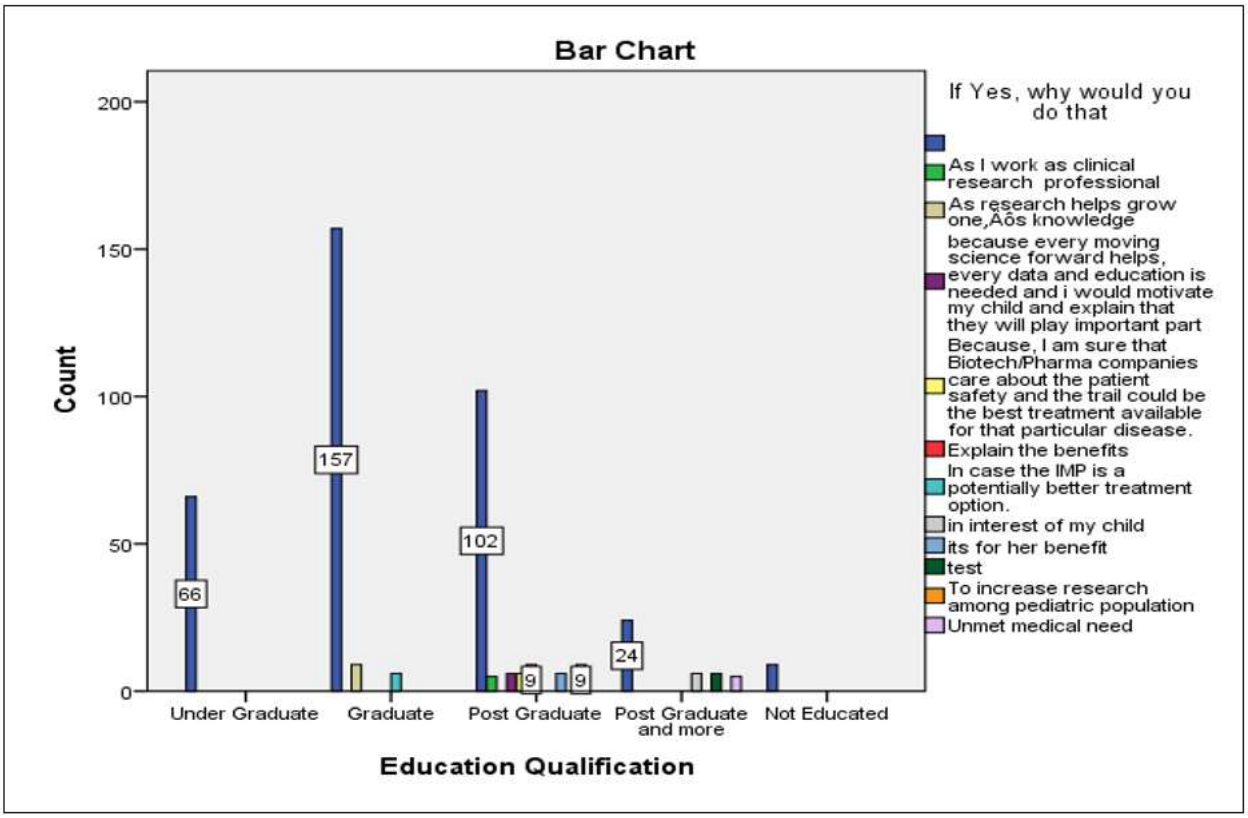
between the ages of 25 to 35 years. Most of the participants were found to be either graduates (39.9%) or post graduates (33.2%), with respect to their educational qualification. 95.1% of the participants were from urban regions. 33.4% of them had an annual income between INR 2,00,000 to 6,00,000, while 26.9% earned more than 6,00,000 and 21.1% earned more than INR 15,00,000 per annum. Majority of these participants (57.3%) were employed in the private sector.

The responses of the participants to the initial part of the survey, which assessed their awareness regarding clinical trials, and the involvement of children in it. Their responses were categorized based on their level of education, and the differences in group-wise responses were tested for statistical significance using Pearson Chi-square test with $p = 0.05$ as cut-off.

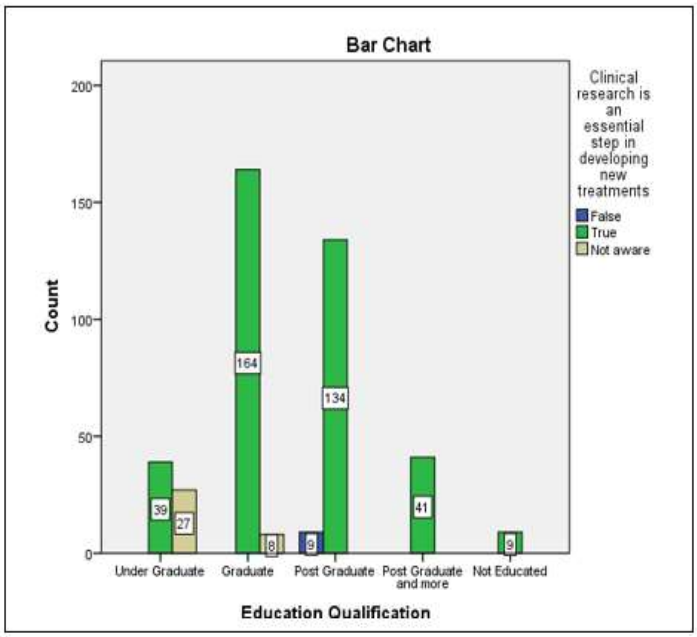
The participants were first asked whether they had heard about clinical trials. To this 317 (73.5%) responded in the affirmative. The responses were plotted with respect to their educational qualification. Majority of the graduates and post graduates had heard of the term, however none of the non-educated participants had heard of it. There were no significant difference observed with respect to the educational level ($\chi2 = 38.82$, $p < 0.05$).

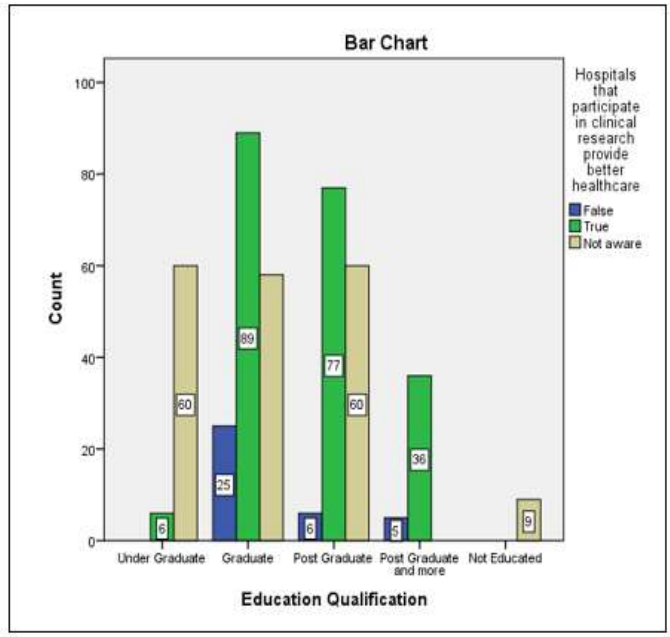
The participants were then asked, 'Would you allow your child to participate in Clinical Trial?' to which majority (67.1%) responded in the negative. When plotted with respect to education levels (fig.8), the negative emotion was present across all groups, irrespective of their level of education. There were no significant difference observed with respect to the educational level ($\chi2 = 33.08$, $p < 0.05$). In the next question, the participants were asked, 'If you are comfortable with your child's participation, but he/ she is not? In that case would you try to convenience your child?'. Again majority of the participants (80.3%) responded negatively, and this trend was irrespective of the participant's level of education. There were no significant difference observed with respect to the educational level ($\chi2 = 52.41$, $p < 0.05$).

The participants were further inquired, what reason can make them convince their child. The most popular reasons given were 'Explain the benefits', 'As research helps grow one's knowledge' and 'To increase research among pediatric population' . The participants were next asked, 'If your child is willing to participate and you are not ready for his/ her participation, would you respect his/ her idea?', to which 259 said 'yes'. Majority of these were post graduates, when plotted with respect to education. However, there were no significant difference observed with respect to the educational level ($\chi2 = 52.41$, $p < 0.05$).



The participants were then asked if they believed that clinical research benefitted the society. To this majority of the participants (89.8%) stated that the statement was true. This awareness was present irrespective of their educational qualification, hence there were no significant difference observed with respect to the educational level ($\chi 2 = 20.81$, $p < 0.05$). The participants were then asked if they felt that advancement of science is reason behind the development of new drugs. Which was estimated to be true by most participants (379 of 431) and there were no significant difference observed with respect to the educational level ($\chi 2 = 100.47$, $p < 0.05$)

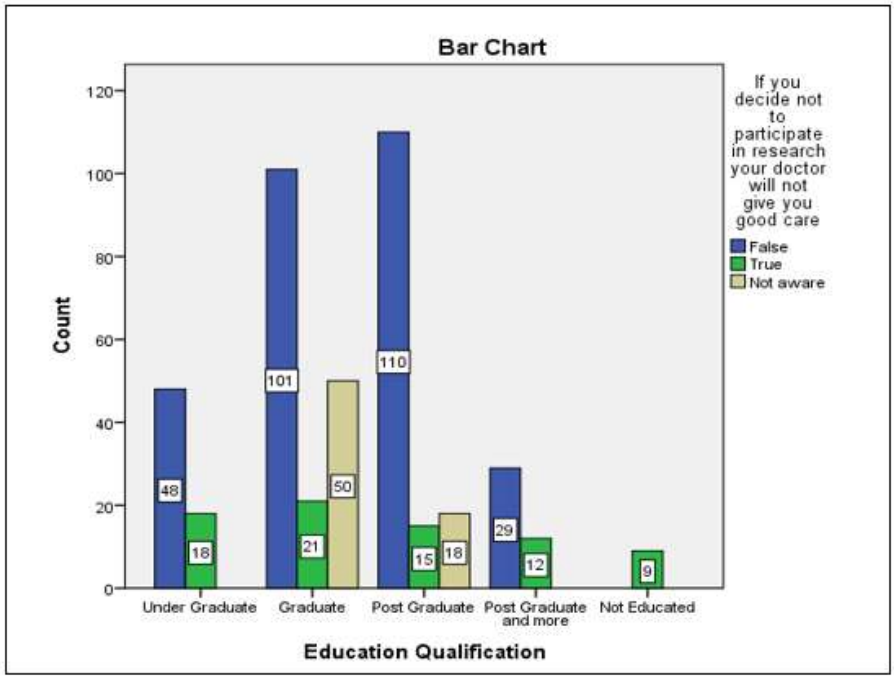




Similar positive attitude to clinical research was displayed by the participants when they were asked, if they thought clinical research is an essential step in developing new treatments. 89.8% of participants felt the statement was true and this sentiment was expressed by all groups, irrespective of their educational qualification. There were no significant difference observed with respect to the educational level ($\chi 2$ = 132.07, $p < 0.05$). The participants were next asked if they thought hospitals participating in clinical trials provided better healthcare. To which, the participants were almost equally divided between 'True' (48.3%) and 'Not aware' (43.4%). There were no significant difference observed with respect to the educational level ($\chi 2 = 120.35$, $p < 0.05$).

When the participants were asked if they thought that, the most important reason for developing new treatments is financial gains, 57.1% of the participants stated that they believed this notion to be false. This sentiment was expressed by all participants across all educational qualifications. There were no significant difference observed with respect to the educational level ($\chi 2 = 55.89$, $p < 0.05$). Next the participants were asked, if the government always adequately protects the public against unethical clinical research. The responses were equally divided, with most stating that they believed it to be true (37.8%) or were unaware (37.6%) of it. The responses showed variation based on educational qualification. However, there were no significant difference observed with respect to the educational level ($\chi 2 = 57.9$, $p < 0.05$). The next question posed to the participants was that, whether they felt that clinical research information provided by pharmaceutical companies can be trusted. The response was once again divisive, as 39.4% felt the statement

to be true while, 39.2% stated that they were unaware of it. This was reflected across the different educational backgrounds. There were no significant difference observed with respect to the educational level ($\chi 2 = 64.77$, $p < 0.05$). When the participants were asked, whether clinical research information provided by academic institutions can be trusted, the divisive response was again observed, with 42.9% stating it was true, and 45.5% stating they were unaware. This was reflected across the different educational backgrounds. There were no significant difference observed with respect to the educational level ($\chi 2 = 104.0$, $p < 0.05$). The response of participants to the statement, if you decide not to participate in research your doctor will not give you good care, is presented in the figure below. There were no significant difference observed with respect to the educational level ($\chi 2 = 97.7$, $p < 0.05$).

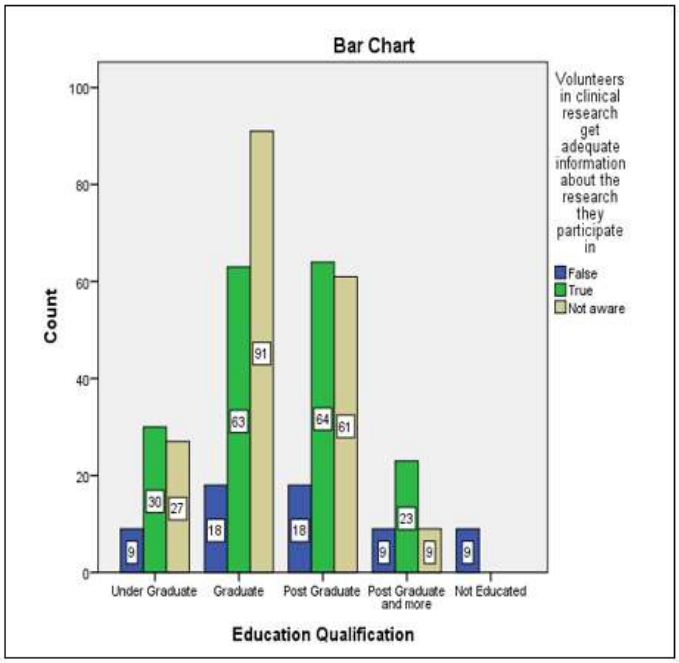


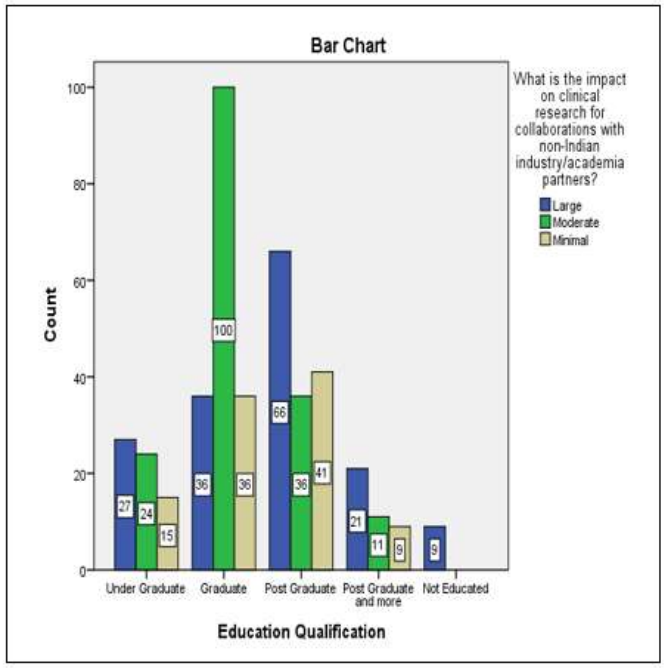
The participants were next asked, whether they thought doctors force their patients to participate in research. 68.4% of the participants stated that they believed the statement to be false. There were no significant difference observed with respect to the educational level ($\chi 2 = 72.71$, $p < 0.05$). Next, the participants were asked if they believed, human participants in clinical research are treated like experimental animals. Majority of the participants (47.6%) stated that they were not aware of such statement. This was most pronounced in case of graduates. There were no significant difference observed with respect to the educational level ($\chi 2 = 77.05$, $p < 0.05$).

When the participants were asked, if participation in research is entirely voluntary, 79.2% believed it to be true. The responses were equally distributed among the different educational qualifications. There were no significant difference observed with respect to the educational level ($\chi 2 = 39.47$, $p < 0.05$). The participants were next asked, if they believed, volunteers in clinical research get adequate compensation for their participation. Most stated that they were unaware of the topic. There were no significant difference observed with respect to the educational level ($\chi 2 = 100.26$, $p < 0.05$).

Next the participants, were asked if they thought confidentiality is a matter of importance to research participants. To which, overwhelming majority of participants (88.4%) found the statement to be true. The response was equal irrespective of their educational qualification. There were no significant difference observed with respect to the educational level ($\chi 2 = 29.98$, $p < 0.05$). When further inquired, if they thought confidentiality of research participants is adequately protected. The response was almost equally divisive between those who thought the statement was true (46.4%) and those who stated that they don't know (41.3%). This distribution was irrespective of educational qualification.

When asked, if they thought results of clinical research are made available to the public, most of the participants (53.8%) stated that they were unaware. This lack of awareness was higher among graduates. Similar lack of awareness (70.8%) was observed in response to the statement, altruism is the only valid reason for participation in research. When asked if the participants thought that, volunteers in clinical research get adequate information about the research they participate in, the response were equally divisive among 'true' (41.8%) and 'not aware' (43.6%). Next, The participants were asked what they thought was the impact on clinical research for collaborations with non-Indian industry/academia partners? Most thought (39.7%) that the impact was moderate.





Discussion

Clinical trials in children are more challenging than those in adults. 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. The current thesis thus investigates which factors are involved in shaping the outlook of the general population, i.e. the parents or guardians of children.

73.5% of the general population were aware of what is meant by clinical trials. The data revealed that there was not much disparity among the surveyed population with respect to their level of education. The rate of awareness seems to have improved in the present data, as compared to previous reports. In a similar survey conducted by Kapadia and Parmar, the rate of awareness was found to be lower at 57.63%10. This increase might be attributed to greater access to internet and social media achieved during the last few years in India. The ratio of being aware was almost same across all groups of the participants.

They were asked if they would volunteer their children for clinical trials, majority of them responded negatively. Their responses remained negative, when they were asked if they would try to convince their

children of joining such trials. This was somewhat contradictory to previous report, where 74.58% of parents had stated that they are willing to respect their children's opinion regarding participation in clinical trials10. Several factors are known to influence how parents seek and process information about a clinical trial and who they decide to involve. The process of informed consent is not just a linear chain of events between the investigators, parents and child, but a very complex experience. Snethen et al. reported that there are three dimensions or factors of decision making in the informed consent process16. The first dimension of the decision-making process reported were parental goals for decision-making. The second dimension was how much involvement the child would have in the decision-making about whether the child would participate in the clinical trial. The final dimension was the role a parent thought they would hold in decision making, and the degree of input they decided they would have.

There was positive attitude and trust towards doctors as majority of parents did not believe that doctors will force the children into clinical trials. This presents that doctors are perceived as being responsible individuals. Majority of parents also stated that they did not believed that participants are treated like guinea pigs in clinical trials. The participants did display lack of awareness when they were asked about confidentiality regarding clinical trial data, compensation for participants, and about volunteers getting adequate information. However, none of the responses in the survey displayed any statistically significant relationship with the education level of the person answering. This might indicate that level of education is not a major factor in controlling people's perception of pediatric clinical research.

Conclusion

The present study was conducted through a questionnaire survey involving parents with focus on issues persisting with recruitment and recruitment rate in pediatric clinical trials. As clinical trials are, perhaps, the most regulated type of research – subject to provincial, national and multiple international regulatory bodies' reference has been made to these regulations, wherever appropriate. The legal framework of clinical trials regulation in India is based upon the ethical principles of good clinical practice and other guidelines. However, it is challenge to ensure those principles are respected in India and if it is, then it is correctly perceived by individuals as they are the ones to be enrolled and are potential to be a trial subject. In this study, we studied perceptions of general population on those ethical principles, issues and conduct of clinical trials.

The conducted research generated a large volume of data regarding how the society as a whole perceives pediatric clinical trials. The study identified the key concerns that exists in the minds of parents while agreeing to volunteer their children for such trials. The study also presents how the different guidelines and the research personnel are viewed by the parents. 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. Trials involving children are on trial. This is particularly alarming at this juncture in health research, when the fruits of our investment in basic biomedical research should be being realized. 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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