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Review Article

Clinical trials in pediatrics-review of ethics and law

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ABSTRACT

Children were acknowledged as 'therapeutic or pharmaceutical orphans' in 1960s, since then there has been a worldwide recognition of the need to conduct clinical trials in children, to improve their health. Prescribing in children is often based on extrapolation of trial results from adults, due to the lack of paediatric data. Children have different pharmacokinetic and pharmacodynamics responses as compared to adults. Hence extrapolating the adult safety and efficacy data and using it for prescribing in children can have disastrous effects. Relevant literature on clinical trials in paediatrics was gathered and scrutinized with emphasis on legal and ethical perspectives. This research is an exploratory attempt which surveys and summarizes previously published studies simultaneously trying to answer few research questions which addresses the current debates and scenario. Common problems encountered during pediatric clinical trials are unnecessary scrutiny of even minimal risk studies, difference in interpretation of research protocol in multicentre trials causing delay in trials, prolonged review process. The proposed changes to overcome the above mentioned drawbacks are standardized data security protections, enforcing universal ethical principles for conducting pediatric trials, sstandardizing adverse drug reaction reporting to regulatory bodies. There is a need to increase the number of clinicians actively involved in pediatric research. All the stake-holders such as regulators, parents, ethics committees, research institutions, investigators, sponsors, media, pharmaceutical companies and scientists have to collaborate to ensure that ethical pediatric research is promoted, equipping them with knowledge needed to provide optimal care to their patients.

Keywords: Pediatric clinical trials, Law, Ethics

INTRODUCTION

Clinical trials are scientific studies carried out to answer specific health questions in human volunteers. Clinical trials are the safest way to evaluate novel therapeutic options on human beings.[1] Children were acknowledged as 'therapeutic or pharmaceutical orphans' in 1960s, since then there has been a worldwide recognition of the need to conduct clinical trials in children, to improve their health.[2,3] Very often prescribing in children is based on extrapolation of trial results from adults, due to the lack of paediatric data. Pediatric age group does not equal to 'little adults,' they are a heterogeneous group, ranging from preterm neonates to post-pubertal adolescents. Children have different pharmacokinetic and pharmacodynamics responses as compared to adults. Hence extrapolating the adult safety and efficacy data and using it for prescribing in children can have disastrous effects.[4] One such example is the thalidomide tragedy, thalidomide was used for morning sickness in pregnant women with destructive effects on foetal development, resulting in thousands of children being born with phocomelia.[5]

Research questions

Following are the research questions-Should children be involved in clinical trials? Ethical and legal implications? If yes, when should they be involved in clinical trials? What are the problems faced during clinical trials?

Informed consent in pediatric patients prior to clinical trial. Off label use of drugs in pediatrics: Ethical and legal implications?

Research methodology

Relevant literature on clinical trials in paediatrics was gathered and scrutinized with emphasis on legal and ethical perspectives. This research is an exploratory attempt which surveys and summarizes previously published studies simultaneously trying to answer few research questions which addresses the current debates and scenario, and possibly fill few gaps in the research.[6]

Purpose of the study

The purpose of the study is to draw attention of all stake holders and emphasize on the importance of pediatric clinical trials. Safety and efficacy data of many drugs used in children are scarce so they are often prescribed drugs based on the data obtained from adult clinical trials, as a result children are exposed to unknown harmful side effects. Hence more scientific pediatric clinical trials are required to improve our knowledge about pharmacokinetics and pharmacodynamics of drugs in children and prevent unnecessary adverse effects in them. Paediatric clinical trials are more challenging to conduct than adult trials because of the lack of financial support, uniqueness of pediatric physiology, and stringent regulations and ethical concerns. Despite 25.7% of the world's population being children, paediatric trials constitute only 16.7% of the total number of trials registered on the world health organization (WHO) portal.[7,8] Although there is slight improvement in the current situation with respect to regulations, quality and the number of trials being conducted in children, there are still lacunae that need to be filled for safe and complete utilization of modern-day treatments.[9]

ANALYSIS OF LEGAL AND ETHICAL IMPLICATIONS IN CLINICAL TRIALS IN PEDIATRICS

Should children be involved in clinical trials? Ethical and legal implications?

Pediatric research has always been ethically problematic. Unlike adults, in children getting voluntary, written informed consent is not possible. Hence investigators, parents, and regulators determine whether the risk-benefit ratio is acceptable and favorable to the participant and whether to go forward with the study. Pediatric research in the United States has special regulations such as, higher level of scrutiny and more stringent protective measures. Pediatric research is essential because children, particularly infants, respond differently to drugs and other medical treatments than do adults. Many drugs, while safe in adults, have serious and even fatal adverse effects in children.[16]

Pediatric clinical trials often require longer follow-up than adult clinical trials in order to identify long-term developmental effects. The current pediatric research guidelines outline four levels of risk. The least level of risk is "minimal risk." Minimal risk is defined as 'the chances and degree of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination'.[17] Clinical trials with minimal risk can be carried out, even if there is no prospect of direct benefit to the research subjects. Consent of one parent and the assent of the child, if the child is old enough and cognitively capable of giving assent is sufficient for such trials. The problem with the classification of risk is, it does not specify whether these risks should be compared with normal, healthy children, or with sick children. A sick child might undergo invasive procedures, treatments, and tests on a daily basis. A normal healthy child is also at risk of being injured when they ride a bike, play sports, take dance classes, or climb trees, but these risks are unlike those encountered in a research study. This vagueness creates subjective interpretations by investigators and institutional review boards (IRBs).[18]

Shah et al found that there was significant difference in evaluation of the level of risk, for example, 23% of the participants felt that allergy skin testing was minimal risk, 43% felt that it was a minor increase above minimal risk, and 27% felt the need to impose more than a minor increase over minimal risk; similar difference was also seen in evaluation of direct benefit.[19] The second level of risk is called "a minor increase over minimal risk." Research with second level of risk even with no direct benefit to the subjects, can still be approved by an IRB, but only if the research is likely to provide important information about the child's disorder. The risks are acceptable if they are in proportion with child's medical, dental, psychological, social, or educational situations. Consent from both parents is needed, as is child's assent. Research with third level of risk involves risks that are greater than minimal or even minor increase over minimal risk but that also directly benefit the child. These studies were previously referred to as "therapeutic research" but that term is outdated now. In such studies, the IRB carries out risk-benefit analysis and determines whether the anticipated benefit justifies the risk. However, these assessments can be subjective.[20]

Consent of both parents and the assent of the child are needed. Conduct of studies that fall into this third risk category is justified by the assumption of "clinical equipoise." Benjamin Freedman described "clinical equipoise" as "a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial." However, these studies are not devoid of merit. According to Freedman, clinical equipoise exists when there is "an honest, professional disagreement among expert clinicians about the preferred treatment." An ethically sound clinical trial should offer reasonable hope of resolving this disagreement. Conversely, if existing evidence clearly

favors one treatment or another, or if the proposed trial is unlikely to disturb the state of equipoise, the trial should not proceed as designed. This is not different for research that involves children. In the initial interpretation of the national commission's recommendations for research involving children, Albert Jonsen described that research should be "valuable and necessary for the health and wellbeing of children."[20]

The fourth risk category is the most complex and the most unusual. They are studies that involve more than a minor increase over minimal risk, no prospect of direct benefit for the child, but are expected to yield vital information which will help in preventing or improving a serious health condition in children. IRBs cannot approve these studies; instead they need to refer them to federal government. Such studies require consent of both parents and assent of the child.[20]

If yes, when should they be involved in clinical trials?

Most of the new chemical entity (NCE) or molecules that enter phase one trials in adults never receive regulatory approval because of lack of efficacy or safety concerns, it is not reasonable to enrol children in drug trials till the sufficient proof of safety and efficacy in adults are available. Hence, it is advisable to conduct pediatric trials only after adult trials has reached phase three or beyond.[21] This may be relaxed, if the disease exclusively occurs in children. For better understanding, the medications can be classified as follows: Medicinal products for diseases that affect children exclusively (e.g., surfactant used for the treatment of hyaline membrane disease (HMD) in neonates). Here, it is logical that the entire drug development program is conducted entirely in children, Medicinal products to treat diseases that mainly affect children, or are of particular gravity in children or have a different natural history in children, Medicinal products intended to treat diseases occurring in adults and children, for which there is currently no treatment and medicinal products to treat a disease occurring in adults and children for which treatments exist, but where there is insufficient knowledge of efficacy or toxicity in children.

For drugs used in severe diseases where there is no proven treatment, pediatric trials can be initiated early, after obtaining safety and tolerability data in adults. For other drugs, pediatric trials can be initiated once efficacy and safety have been studied and proved in adults[22]. Initiation of pediatric studies depends upon the severity of a disease and availability of alternative therapies. Fatal congenital genetic or metabolic diseases have no analogy in adults and hence not possible to generate adult efficacy data. Nevertheless, it is advised to obtain initial safety data in adults before pediatric testing.[21]

What are the challenges faced during pediatric clinical trials?

Ethical issues arising from the research design

When a drug is being used for a neonatal condition, in an off-label manner, without high level of evidence and a clinical trial is planned; choosing the correct control (placebo for placebo-controlled trial, PCT; or active drug for active controlled trial, ACT,) becomes important. An active control/ drug can be used only if the study drug has been proved to be more efficacious than placebo. For a drug used without such evidence, ACT is not advisable. If both the study drug and active control are shown to be equivalent; it is possible that both are ineffective or only marginally effective. Such trials, therefore, could continue the use of therapeutic agents that are ineffective or have small benefit-to-risk ratio. Some recommend that except in life-threatening situations, ACT should only be undertaken when the superior efficacy of the active control over the placebo has been established. If this has not been demonstrated, one can conduct a three-arm trial (administration of a placebo, administration of experimental drug and administration of an active comparator) or an "add-on" trial. [23]

PCTs are carried out, when no proven active treatment exists, or the standard treatment is extremely toxic and majority of parents refuse therapy because of its toxicity. Even when proven therapy does not exist, investigators think that the patients in placebo arm are receiving an 'inferior treatment' when compared to active control/drug arm, and this raises an ethical dilemma. This can be rectified by adopting randomization scheme that has unequal allocation; or using a fully sequential design with equal group allocation or using one of the response adoptive designs ("play-the-winner" or "drop-the-loser" technique). In these techniques the probability of being assigned to the (currently) superior treatment is greater than 50%. When the standard treatment is effective and is not associated with any serious side effects, a PCT can be justified only if the risk of placebo is limited to minor and temporary discomfort and proper informed consent is obtained; and there exists a compelling scientific justification to conduct the study using a placebo and if valuable knowledge can be gained and investigators have disclosed the administration of a placebo. The most challenging ethical dilemma in conducting PCTs of drugs used off-label arises when only grade II-III evidence for efficacy exists. One of the controversial aspects of the use of placebo in a given situation is the trade-off between the risks to the subjects and the potential benefit to society. Hence it is advisable not to routinely recommend PCTs for drugs used off-label with grade II evidence supporting their efficacy.[23]

Ethical issues with enrolment of subjects

Seeking informed consent from parents when clinical equipoise exits creates a barrier to enrolment in the trial. For instance, in a hypothetical situation, wherein the doctor believes that a particular drug is effective and uses it in his or her practice to treat a particular neonatal condition. In such a situation, the doctor is obligated to inform the baby's parents regarding his or her preference

for that particular drug in the baby's best medical interests; creating a barrier to enrolment in the trial. This can be resolved by the doctor explaining to the parents that although he/she prefers a particular drug, there is insufficient evidence to support its use and that there is a lot of disagreement in this regard in the expert medical community. Therefore, it is necessary to conduct a formal study to settle this dispute. From an ethical viewpoint, the doctor is obligated to offer the parents the opportunity to enrol their baby in an RCT.[23]

Informed consent in paediatric patients prior to clinical trial

Informed consent acts like an armour of protection for research subjects, even for children. Parents or legally accepted representative (LAR) are responsible for providing permission or consent for participation of their child in a research study. In the USA, research involving minimal risk or one which benefits the child requires consent from only one parent; while other categories of research require permission from both parents. Parents or LAR can act in the best interests of their children when there are no undue financial incentives for participation and when they are well informed. Investigators often feel that parents are overburdened with information and are reluctant to educate the families about trials, but in reality, parents may view trial participation as an exciting opportunity. As the parents make their trial decisions based on their child's safety, well-being and benefits to the child, they should be provided with enough information to make an informed choice. Article 7 of the international covenant on civil and political rights (ICCPR) recognizes that a lack of informed consent constitutes a human rights violation [24]

In addition to obtaining parental permission, child's assent is also a must; which has been described as "affirmative agreement to participate in research." As per the ICMR Guidelines assent should be obtained from children aged 7-18 years.[25] In some countries, the Ethics Committees determine whether assent is required or can be waived after considering the age, maturity and psychological state of the participants. The ECs determine if all children in particular research should assent or that children above a particular age should assent. Assent process must be age and maturity appropriate. It should be an empowering and respectful experience. Children have to be informed about their condition, about the whole trial process, the potential benefits and risks and then take their assent to participate.[26]

Separate age-appropriate parent or LAR and participant information sheets; and consent, and assent forms should be prepared.[22] Most of the investigators and Ethics Committees prefer written documentation even though assent need not include a written form or signature. There is great variability in implementing the assent process because the process is left to the discretion of the ECs.[27] Assent need not be sought if the beneficial intervention is available only on participation in the research study. However, they have to be informed about the research study and procedures.

There is no consensus amongst various international and national guidelines regarding what an 'assent' really means. The argument is children are not capable of making life changing decisions. Parents make that decision on their behalf, often in the interests of their child, but they do consider the interests of others in the family. [28]

There is also disagreement about the age of assenting being seven years. Considering only the chronological age is not acceptable because how can a seven-year-old child with mental retardation and mental age of three years be expected to assent to participation? Assent is emphasized only in research, but ignored during treatment. Both parent and child should consent and assent respectively in order to participate in a trial. Any disagreement by either of the party can cause conflicts within the family and strain relationships.[28,29]

In many neonatal trials, the enrolment should occur at or soon after birth. This raises ethical issues similar to those in emergency research. Seeking consent within a short period of time causes parental distress; it might violate the principle of autonomy and tempt investigators to give incomplete information, questioning the validity of the consent process.[30]

The ethical issue may be resolved by seeking exception from informed consent process requirements (by invoking the regulations for emergency research); obtaining waiver of consent (from the EC) or by obtaining consent during the antenatal period. The last option seems to be most appropriate, when the relevant national research guidelines do not provide detailed safeguards or steps for invoking the first two options. Even when the consent has been obtained during the antenatal period, the parents should be informed as soon as the neonate is involved in the trial. In a less studied opt-out system, the parents' consent is presumed following antenatal discussion unless they had refused to participate antenatally or after inclusion of their baby in the trial. Some argue that such a process will lessen parental distress and will be socially acceptable when conducted during less hurried and frightful circumstances than when conducted after delivery of a sick infant. The opt-out system may be kinder by allowing more than enough time to opt-out and by decreasing the burden of having to decide whether or not to consent.[23] Many neonatal trials are associated with high rate of mortality. However, few trial teams have had responses to bereavement in place. It may be a good idea for research teams to develop and assess responses to the bereavement.[31]

Off label use of drugs in pediatrics: Ethical and legal implications?

Prescribing medications for an indication, or using a dosage or dosage form, that has not been approved by the

FDA is considered as Off-label drug use (OLDU). Other terms used for OLDU are unlicensed, compassionate use and non-licensed drug use (NDU). OLDU is more common in areas of medicine in which the patient population is less likely to be included in clinical trials (e.g., pediatric, pregnant, or psychiatric patients). The most common form of OLDU involves prescribing currently available and marketed medications but for an indication (eg, a disease or a symptom) that has never received food and drug administration (FDA) approval. Hence, the specific use is "off-label" (i.e., not approved by the FDA and not listed in FDA-required drug-labelling information). The term OLDU can also apply to the use of a marketed medication in a patient population (eg, pediatric), dosage, or dosage form that does not have FDA approval.[32]

The best pharmaceuticals for children act (BPCA) and the pediatric research equity act (PREA) has made more than 500 pediatric labeling changes. Off-label use of drugs is a complex issue in preterm and full-term neonates, infants and in children less than 2 years, and children with chronic and/or rare diseases. [33]

The BPCA and the PREA have substantially increased clinical trials and labeling of drugs in children by the pharmaceutical industry as well as through government-sponsored trials. The PREA mandates that almost all new drugs and certain approved drugs must be studied in children if there is potential for use of that drug in children and the new drug approval application must include results of adequate pediatric studies unless waived by the FDA. The sponsors are allowed an additional 6 months of market exclusivity by the BPCA, if the sponsor completes and submits pediatric studies results to the FDA. Specific drugs are evaluated in children based on prioritization done by National Institutes of Health, the FDA and doctors from various specialties who are authorized by the BPCA. The National Institutes of Health then petitions proposals for pediatric drug testing and funds clinical studies that are judged by external review. The approval of these 2 laws has brought about more than 500 pediatric labeling changes. Also, there is increased prospective pediatric drug testing by industry-sponsored studies, investigator-initiated studies, and consortia, such as the national institute of child health and human development–funded pediatric trials network resulting in expansion of both pediatric labeling information and the knowledge base from which practitioners can draw to make informed therapeutic decisions. In 2012, the BPCA and PREA were reauthorized by the food and drug administration safety and innovation act. Main goal is to conduct pediatric trials earlier in drug development process and to improve the neonatal drug studies under BPCA and PREA. Legislation also makes both BPCA and PREA permanent law.[33]

DISCUSSION

Levanthal et al found that the common problems encountered during pediatric clinical trials are unnecessary scrutiny of even minimal risk studies, difference in interpretation of research protocol in multicentre trials causing delay in trials, IRB not in consensus with respect to benefits, interventions and the overall acceptability of the trial resulting in prolonged review process, limited background knowledge of IRB members with limited time and resource adds to the problems.[34] Complex informed consent documents filled with technical terms mainly intended to protect institutions rather than inform and protect children and their parents. Development of protocols which mainly focus on technicality rather than protecting the subjects. Protocol approval does not mean that the study is ethical, and an ethical study does not always guarantee an approval. The proposed changes to overcome above-mentioned drawbacks were standardized data security protections, this will reduce excessive scrutiny of minimal risk studies limited to assessment of previously collected data or samples. Enforcing universal ethical principles for conducting pediatric trials. Standardizing adverse drug reaction reporting to regulatory bodies. Designing informed consent forms in such a way that it contains all necessary information in simple understandable language required to make a decision favourable to their child. Waiver of informed consent for studies using de-identified bio-specimens. Multi-center studies can be reviewed by multiple IRBs; this will improve quality of research oversight.

CONCLUSION

Pediatric clinical trials provide valuable information to the clinicians. It is essential to carry out pediatric clinical trials to ensure that better therapies become available to them. However, with proper planning and additional safeguard measurements ethical research can be conducted in children. Although the number of clinicians involved in pediatric research has grown, there is a need to increase the number of clinicians actively involved in pediatric research. All the stake-holders such as regulators, parents, ethics committees, research institutions, investigators, sponsors, media, pharmaceutical companies and scientists have to collaborate to ensure that ethical pediatric research is promoted, equipping them with knowledge needed to provide optimal care to their patients.

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