

Perspectives of Children Being Considered as Vulnerable Subjects in Clinical Trial

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Abstract:

Knowledge of clinical trials are valuable irrespective of science to gain information about a disease, its condition, drug or treatment that will benefit the human race in future. The issue of Good Clinical Practice (GCP) and ethical consideration for involving humans in clinical trials has gained increased attention and awareness in order to protect the innocents from untoward incidents and effects. While categorising the group of individuals who are termed as Vulnerable, Children are often considered as first. An assortment of research designs have been evolved these days by keeping in view the safety standards for both individuals involved in the research and the researcher. Various regulating bodies worldwide have defined a set of rules and regulation for conducting clinical trials in order to prevent untoward incidences and misuse of human beings in researches. Every researcher and research organisations are required to follow the same and obtain necessary permissions before starting the trials. The current endeavour is an attempt to bring out the viewpoints based on which the children are considered so and the care to be taken while enrolling them in a research work.

Keywords: Children, Clinical trials, Vulnerable Subjects

Introduction:

A study claims that 70 percent of the medicines given to children have only been tested in adults. [1] However involving children in research raises serious ethical concerns, largely because their autonomy and competence to give informed consent is less than that of adults. But restricting children's participation in research is not appropriate. The usual approach to designing a study that involves children is to conduct preliminary studies in animals, adults, and older children, before young children are involved. There are some experimental interventions, however, in which data may not be entirely generalizable from older subjects, such as treatment of diseases of prematurity. [2]

Ayurveda has too emphasized much on ethical guidelines while treating a patient through medical or surgical interventions. Utmost priority has been accorded to ethical issues and prior consent of the patient has been suggested in various Ayurvedic texts. [3, 4, 5] Further the qualities of a physician, drug, supporting Para-medical staff and role and responsibilities of the patient to achieve success in managing a patient [6, 7] have been enlisted.

As investigators design and implement research protocols, they should be aware of the ethical and legal requirements that govern research with human participants. This is especially true of research that involves children and other vulnerable groups. The job of pediatrician and those

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dealing with children is said to be a tedious job [8] and they are required to be sharp and quick in dealing with their health. The welfare of children participating in research depends on knowledgeable, caring, and responsible investigators who place the well-being of the research participant above all other aspects of the research project. [9]

Materials and Methods:

The guidelines for conducting research on vulnerable subjects which includes children were taken from various regulatory agencies like FDA (*Food and Drug Administration*), ICH (*International Conference on Harmonisation*) and concepts from classics of Ayurveda. The whole article is divided into two parts. The first part deals with reasons for which the children are grouped into vulnerable category and second part deals with the guidelines to be followed while including children for research.

Vulnerable Subjects:

The term 'Vulnerable' is defined as exposure to the possibility of being attacked or harmed, either physically or emotionally [10] and 'Vulnerable Subjects' are those groups that may contain some individuals who have limited autonomy i.e. they cannot fully appreciate or participate freely in the consent process. Such groups include-

1. Children
2. Pregnant women and fetus
3. Mentally ill persons
4. Terminally ill or hospitalized patients
5. Students and employees
6. Elderly persons
7. Prisoners

Children are considered a vulnerable research population because their intellectual and emotional capacities are limited and therefore, they are legally incompetent to give valid informed consent.[11]

They are also unique in many ways. They differ anatomically, physiologically and psychologically with adults. Pre-term newborns, or those born prior to 36 weeks of gestation, present special challenges due to their potentially low birth weight, very immature organs and renal and hepatic clearance, respiratory complications, rapid maturation and other issues. Newborns, which generally fall between birth after 36 weeks of gestation and 28 days

of age, have an immature blood-brain barrier that must be accounted for, as well as immature organs that change rapidly during the first few weeks of life. Infants, who are two to 24 months in age, continue to present challenges due to their rapid growth, and they also present administration difficulties due to their inability to ingest. Children, who technically range from two to 11 years of age, require careful monitoring of cognitive and motor development as well as skeletal growth and weight gain to ensure that the trial is not adversely affecting them. Additionally, younger children often experience needle phobia, stranger anxiety and other factors that can make obtaining their cooperation a challenge. Adolescents or those who age 12 to 18 years, experience hormonal swings that can impact clinical studies, and must be monitored for any adverse effects on sexual maturation. Additionally, privacy is of high concern to this age range, and care must be used when discussing matters such as the use of birth control during a trial. Compliance is also a challenge with adolescents and can require special incentives and monitoring. [12]

According to FDA (Food and Drug Administration)

"Vulnerable Subjects/Participants" mean individuals who lack the capacity to provide informed consent or whose willingness to participate in research may be subjected to undue influence or coercion. [13]

According to ICH (International Conference on Harmonisation):

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate.[14]

Permitted Categories for Research with Children:

Federal regulations classify permissible research involving children into four categories based on degree of risk and type of individual subjects. These categories are described in relation to 'minimal risk':[11]

1. Research not involving greater than minimal risk (45 CFR 46.404 and 21 CFR 50.51)

- a. Permission from at least one parent/guardian

required

B. Assent of the child (if child is 7 years of age or older) required

c. Expedited level of review necessary

2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (45 CFR 46.405 and 21 CFR 50.52):

The risks must be justified by the anticipated benefits; and the risk to benefit ratio must be at least the as favorable as alternative treatments or approaches.

a. Permission from at least one parent/guardian required

b. Assent of the child (if child is 7 years of age or older) required

c. Full Committee (Institutional ethics and review boards) review necessary

3. Research that involves more than minimal risk and presents the prospect of no direct benefit to individual subjects, but generalizable knowledge (societal benefit) (45 CFR 46.406 and 21 CFR 50.53):

The risks represent a small increase over minimal risk;

The interventions or procedures are commensurate with those associated with the subjects' actual or expected medical, dental, psychological, social or education situations; and

The interventions or procedures are likely to yield generalizable information about the subjects' disorder, condition, situation, which is of vital importance to understand or ameliorate.

a. Permission from both parents/guardians required*

b. Assent of the child (if child is 7 years of age or older) required

c. Full Committee review necessary

4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407 and 21 CFR 50.54):

a. Permission from both parents/guardians required*

b. Assent of the child (if child is 7 years of age or older) required

c. Full Committee review necessary

d. Requires submission to the Secretary of the Department of Health and Human Services who after consultation with panel of experts and following an opportunity for public review and comment must either approve or deny approval of the study.

e. This type of study is very rarely approved.

*Unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. If these circumstances are present, the researcher should document this in the subject's research record.

Guidelines for Selection of Special Groups (Children) as Research Subjects

Before undertaking trial in children the investigator must ensure that

Children will not be involved in research that could be carried out equally well with adults;

The purpose of the research is to obtain knowledge relevant to health needs of children. For clinical evaluation of a new drug the study in children should always be carried out after the phase III clinical trials in adults. It can be studied earlier only if the drug has a therapeutic value in a primary disease of the children;

A parent or legal guardian of each child has given proxy consent;

The assent of the child should be obtained to the extent of the child's capabilities such as in the case of mature minors, adolescents etc;

Research should be conducted in settings in which the child and parent can obtain adequate medical and psychological support;

Interventions intended to provide direct diagnostic, therapeutic or preventive benefit for the individual child subject must be justified in relation to anticipated risks involved in the study and anticipated benefits to society;

The child's refusal to participate in research must always be respected unless there is no medically acceptable alternative to the therapy provided/tested, provided the consent has been

obtained from parents/guardian;

- Interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual child subject as any available alternative interventions;
- The risk presented by interventions not intended to benefit the individual child subject is low when compared to the importance of the knowledge that is to be gained. [15]

Assent:

Children are legally unable to give valid consent, but they may possess the ability to assent to or dissent from participation. Out of respect for children as developing persons, children should be asked whether they wish to participate in the research, particularly if the research is unlikely to be of benefit and the child can comprehend and appreciate what it means to be a volunteer for the benefit of others. If the research could directly benefit the child, assent is not required.[2]

The information given to the child should be age-appropriate, understandable, and tailored to the child's emotional and cognitive maturity. Dissent should be honoured, and children should be allowed to withdraw at any time. The ability to give assent requires cognitive ability and the ability to engage in abstract thinking, which depends not on chronologic age but on developmental achievement.

- Assent is defined as a minor's affirmative agreement to participate in research.
- In most cases, this must be documented in writing if the subjects are at least seven years old.
- May require assent from children younger than seven if they are likely to comprehend and appreciate what it would mean to volunteer to participate in a given protocol.[11]

Written Assent Requirements

Assent forms should be written at the appropriate educational and maturity level of the youngest prospective subject in the age range.[11]

Techniques such as the use of larger type, simple schema, and pictures may help boost a child's understanding of the text.

Depending on the age range of the minors to be involved, the Lead Researcher may be required to develop 2 different assent forms at different reading

comprehension levels (e.g., one assent form written for young children aged 7-12 years old, and one assent form written for minor's ages 13-17 years old). Alternatively, for children 13-17 years of age, the researcher may develop a joint assent/permission consent form and obtain the signatures of the minor and parent(s) or guardian(s) on one document.

Assent Elements

An assent form should contain date and signature lines for the child, a witness, and an investigator. The assent form should cover the following points:

- What the study is about,
- Why the child is eligible to participate for the study,
- What procedures will be performed,
- Potential risks and discomforts to the child,
- Potential benefits to the child and society,
- For non-therapeutic research, a statement that the child can choose whether to participate and may withdraw at any time without negative consequences,
- An invitation to ask questions any time, and
- Names and phone numbers of whom to contact with questions.
- Because children cannot legally provide consent for research on their own behalf, permission by at least one parent or legal guardian is required prior to enrollment of a minor in a research study. [11]

Discussion and Conclusion:

Clinical research in children helps us to treat our children like children, rather than little adults by [16] finding the best dose of medicines to prevent harmful effects or under-treatment. It helps us to protect children from untested, potentially harmful practices and to give access to new drugs or treatments like making chewable, liquids or tablets that are easily palatable for children to take, yet still safe. Finding treatments for problems that occur only in children, like prematurity and other treatments for diseases or conditions that occur in both children and adults but which can act differently in children and adults, like arthritis or heart disease is possible only through clinical trials done upon children. Identifying treatments for new or existing diseases to improve the health of children in the future, like vaccine studies

that were done years ago help children stay healthier today.

However involving children in research raises serious ethical concerns, largely because their autonomy and competence to give informed consent. But restricting children's participation in research is not appropriate either. Adapting a distinct safety protocol and making an allowance for obtaining the legal clearances, clinical trials on children must be carried out keeping in view of benefits they have or the future generations would receive through their participation in the trials.

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