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EDITORIAL

Involving Children in Clinical Research: Ethical Dilemmas and Perspectives

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Progress in children's healthcare can only be achieved through research, which forms the evidence base for interventions to protect them from ill health, disease, and the impacts of disability (1,2). Given the methodological and ethical challenges of research in children, there are tendencies to extrapolate information from adult studies, which often poses several problems. There are differences in disease processes and the effects of interventions between children and adults. The pharmacokinetics of many drugs and their beneficial and adverse events in children are different from those in adults (3). Young children do not tolerate some drugs and dosages and administration of the drugs may be difficult. These differences and the fact that many adult diseases have antecedents in early life and their occurrence in adults can be prevented with effective evidence-based strategies in childhood make clinical research in this age group imperative (4).

In research involving children, the need for the research and whether children need to be involved should be the primary consideration. Balancing the protection of this vulnerable patient population with the need to do clinical research to improve their health and well-being constitutes one of the quandaries of clinical research in children. The core ethics principles (beneficence, nonmaleficence, autonomy, and justice) in research that relate to adults apply equally to children (5). However, research with children gives rise to a wide range of unique and complex ethical challenges and dilemmas (6). The increase in international research collaborations and the context in which research is conducted also constitute critical ethical challenges.

An ethical research must produce reliable and valid data that can be interpreted. Indeed, an underpowered study, a study with a biased endpoint, instrument, or statistical test, and a study that cannot enroll sufficient subjects is invalid and unethical (7). Research that is good for children needs to answer an important question for the research subjects in this age group and carry an acceptable risk to the subjects. Before starting the research, one needs to answer an important question

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for the research subjects in this age group and carry an acceptable risk to the subjects. Before starting the research, one needs to carry out a risk assessment, particularly considering the risks of harm to children and ways to mitigate, monitor, and manage the risks. It is paramount to recognize that children on the age spectrum from the newly born to adolescence have different experiences and roles concerning decision-making and that, when they are ill, the nature and severity of illness may be specifically important as are the wider social and economic factors.

It is well recognized that respect for autonomy (informed consent, truth-telling, and confidentiality) in research related to children constitutes the most challenging ethical requirement to meet giving rise to complex ethical dilemmas (8). As with medical treatment and as far as possible, children should understand the nature and what will be expected of them before taking part in the research. It is important to explain confidentiality to the child before they give their consent (the positive agreement of the parent/guardian). According to the Declaration of Helsinki (9), when possible, the child's consent/assent should be obtained in addition to parental consent. Emancipated minors—working or earning their living, married, parenting—may be allowed to give informed consent or an institutional review board (IRB) may decide a waiver of consent (10).

In addition to the consent of the parent, next-of-kin, or guardian, assent (a child's affirmative agreement to participate in the research) should be sought from all children 12 years of age and above (10). The default threshold age for assent is 7 years in some guidelines, but there are differences, and a flexible criteria for personalized threshold age determination is suggested (11). In institutionalized children, a legally approved guardian may give consent. Assent with waiver of consent may be applicable in research dealing with sensitive issues like drug use and abuse and sexuality to avert problems for the child because of the nature of the study. Children should be given appropriate information based on their level of comprehension irrespective of the complexity of the research procedures. The extent to which the information, however clearly presented, can be received, considered, and understood by parents poses a major challenge in obtaining consent. The process of consent requires that time be available to reflect on whether to agree to participate, but that may often not the case sick children.

In clinical trials, it is exceedingly difficult to explain that a new treatment is unproved but potentially valuable, gain consent for entry into the trial, and then explain that the patient has been randomized to standard therapy, while still maintaining parents' trust (12). As an alternative, the parents may be informed before their child was enrolled in the study and they could refuse permission for their child to take part. With this approach, the potential benefits of research would be maintained, while ensuring that there was minimal risk would be placed firmly on the

researcher and ethics committees. Children should also be protected from bearing more than their fair share of the burden of participation in and be assured of the benefits of research (13)

In the context of developing settings, those who conduct research with children invariably adopt western concepts and approaches that may not largely address the needs of children in these settings. This is a paradox as only a little more than 10% of the world's children live in the developed countries and yet related research is heavily concentrated on children from developing countries (14). Inherent in globalization, much of the penetrating research work is sponsored by external funders applying research paradigm rooted in Western ethos. As emphasized in a study report from Ethiopia, the development of participatory-based paradigms and ethical approval procedures need to guide research with children in the global south (15).

Ethical issues of research with children are embedded in diverse and shifting paradigms. An efficiently administered, effectively performing system with adequate resources to meet ethical and legal standards for protecting children (and adolescents) who participate in research. Pediatricians practicing in Ethiopia, and those particularly working in tertiary care centers, need ethical guidance and training in order to care for critically ill patients while upholding the highest ethical standards and deal with ethically complex situations. The Ethiopian Journal of Pediatrics and Child Health (EJPCH) of the Ethiopian Pediatric Society (EPS) upholds that any research undertaking should be approved by a relevant institutional review board or ethics committee. It observes that ethical considerations are adequately covered in its publications. EJPHD believes, supports, and encourages that due considerations are given to research in children (and adolescents) by pediatricians, researchers, managers, regulators and policy makers.

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