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SYMPOSIUM

Ethical Issues in Prospective Studies in Children: The many Shades of Gray

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ABSTRACT

Children being a vulnerable, unique, yet heterogenous population, pose varied ethical questions in clinical research. These need to be actively recognized and addressed in order to strike the right balance between 'individual' good and 'societal' good. Certain general principles which can be streamlined into guidelines specific for each population and study is the need of the hour.

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INTRODUCTION

Children, as such, are a vulnerable population in clinical research. As it has been repeatedly quoted in multiple contexts, rather than being 'small adults', they are a heterogenous population, a continuum of different ages and stages of development rather than multiple age-based subgroups. From the premature newborn to an adolescent undergoing transition to an adult, as in diagnosis and therapy, they pose numerous challenges in clinical research too. The heterogeneity and the vulnerability make ethics a special concern, as it is illustrated by the following two examples.

EXAMPLE 1

With the increasing incidence of chronic noncommunicable diseases, like type II diabetes, hypertension, hyperlipidemia and cardiovascular diseases, and the threat of a full blown epidemic looming large over developed and developing countries alike, preventive strategies, focussed mainly at the younger population are being researched upon. The research participants in such studies are children, including young babies who are a part of birth cohorts.[1]

There have been multiple such studies[2,3] which have followed thousands of children through their infancy and childhood into adulthood in an attempt to identify or confirm potentially remediable risk factors; some known, and others, lesser known, lurking in the 'nature' or 'nurture' of the child and looming in the adult, in whom little can be done to uproot the causative factors at work. One such factor that has consistently been shown to be associated with the above-mentioned chronic diseases is obesity, which also, has been shown to track into adulthood. Studies which seek to establish the long-term effects of obesity in early life raise several ethical issues. While there is no doubt that such studies could make vital contributions to 'societal good' in the long run, can 'individual good' of the research participants too be ensured? This question is especially important in the above context since the research participants here constitute a vulnerable population.

EXAMPLE 2

Another good example in recent times, that highlights the importance of a valid informed consent is the controversial human papilloma vaccine (HPV) demonstration project that was launched in Andhra Pradesh and Gujarat, in association with the Indian Council of Medical Research (ICMR) and PATH (Program for Appropriate Technology in Health) International, a US-based nonprofit organization. Out of the 23,000 girls that were vaccinated, there were seven deaths, creating a furor among the general public and womens' organizations. Though the probe panel concluded that the deaths were unrelated to the vaccine *per se*, certain glaring lapses in the design of the project and ethical issues of consent were uncovered and the project had to be suspended.[4] In one of the schools in Andhra Pradesh, the participants included a vulnerable group of tribal girls staying in a boarding school, who were displaced from Chhattisgarh due to ongoing conflict.[5] In many instances, the school authorities had given consent *en masse*, without the knowledge of the parents. The information brochure and the consent forms were in English or in Telugu, both of which the girls could hardly comprehend. Various probes following the deaths revealed the discrepancy in the information provided to the girls and/or the parents, right from 'a vaccine that prevents fever', 'a vaccine that would prevent cervical cancer lifelong', to 'an expensive vaccine being given free of cost, which the parents should make use of'. Reporting of adverse events was also poor. This being the case, one becomes sceptical whether all the girls and their parents actually understood terms like 'cervix', 'cancer', 'vaccine' and 'prevention' and their role in the project in order to give a valid and meaningful consent. Moreover, such events not only leave a lasting impact on

the psyche of the layman but also tarnish the image of clinical research.

Prospective, longitudinal, cohort studies are considered to be the ideal research tool in clinical research in establishing an association between a risk factor and disease. They provide evidence of a superior quality when compared to retrospective studies or case control studies. If a statistically significant association is found, true causalty can be established using the Bradford Hill criteria.[6]

The Bradford Hill criteria, also known as Hill's criteria for causation, are the minimal, essential, prerequisite to provide adequate evidence of causalty in a prospective study. These include the following:

1. Strength of association (relative risk, odds ratio)
2. Consistency
3. Specificity
4. Temporal relationship (temporality)
5. Biological gradient (dose-response relationship)
6. Plausibility (biological plausibility)
7. Coherence
8. Experiment (reversibility)
9. Analogy (consideration of alternate explanations).

The larger the sample size and longer the period of observation, better the strength of association and the quality of evidence.

This brings two diverse aspects at loggerheads, one of providing quality evidence and the other of preserving ethical tenets in a vulnerable population. Are these truly contradictory or can complement each other becomes an important question. Is the answer to this question in black and white?

The ethical components of any longitudinal study would include:

1. Informed consent
2. Risk benefit ratio
3. Therapeutic misconception.

INFORMED CONSENT

The following requirements must be satisfied for an ethically satisfactory informed consent:[7]

1. Competence (to understand and decide)
2. Voluntariness (in deciding)
3. Disclosure (of material information)
4. Understanding
5. Decision and
6. Authorization.

All the above parameters are in turn affected by multiple socioeconomic, educational, cultural, environmental and linguistic factors. The aspect that is probably most affected by the dynamic nature of child development is competence, the ability to understand and decide. This in turn depends on not only the age and mental abilities of the child but also on the nature of the study. Is it possible to objectively assess which child is truly competent and at what age?

What if a child, whose parents had initially consented to the study, 'gains' competence during the study period and then decides otherwise? Is the initial consent of the parents still valid? Beyond what age should children be given autonomy to give consent themselves? It is obvious that there can be no uniform criteria since there can be no objectivism to 'maturity'.

Both the quantity and the quality of the information that is provided to the research participant is crucial. It is said that the quantity of information for a valid informed consent need not necessarily be complete (the 'all relevant information' view) but has to be adequate (the 'self management' view) depending on whether the subject chooses based on the information he/she wants rather than what he/she would choose having all the relevant information.[8]

In the first example cited above, the information would definitely include the harmful effects of obesity, both on the child as well as on the future adult, which is the very essence of the study in the first place. In such a case, would not the parent or the legal guardian want to know what can be done to prevent such effects on the child? How were these questions tackled? Even if such questions were not asked, would it not be unethical not to offer therapeutic advice or alert the family practitioner regarding this? In future, would the obese adult, who was once an obese child, whose parents had consented to an observational study to be performed, with no active intervention whatsoever to tackle the obesity, be comfortable with the parents' decision? In retrospect, would the obese adult be willing to give consent if she was legally competent to do it? Will she be now willing to give consent to a study which will enroll her own obese children?

Worse than not being offered therapeutic advice is, probably not even being informed what untreated obesity in the long-term can lead to.

Needless to say, any therapeutic intervention or information would affect the validity of the study results. Children needing intervention would then need to be excluded, considering the 'noninterventionist' nature of such studies. This leaves us with the perplexing issue of the content of information that is to be divulged. It is said that researchers need to balance the crucial need to minimize sample attrition (retain the participants) with the humane instinct to offer health advice, especially if it is requested. With the wide social, economic and cultural differences and the varied age group among the research participants,

especially in developing countries, achieving this precarious balance would remain a challenge.

Finally, more important than whether the answer is 'yes' or 'no', is the reason why it is so. Did the parent truly analyze the information provided and decided in the best interest of the child? Does the child understand what has been told? How do we assess that the understanding has been appropriate and the decision rational? For instance, in a study on European cancer patients agreeing to genetic research, the authors observed that direct interaction with the patients during their hospital stays after surgery, lack of knowledge about genetic research and the desire to please their physicians were the factors that led to a high consent rate.[9] On the other hand, in a larger perspective, a misinformed dissent is probably as much a loss to clinical research and 'larger good'as is a misinformed consent to individual integrity.

RISK BENEFIT RATIO

An equally, if not more, complicated ethical issue in longitudinal studies is calculating the risk benefit ratio and worse, conveying it to the research participant.

'Risk' could entail, either an objective risk to the individual, like undesirable side effects, prolonged suffering, or worsening of the disorder, or subjective burdens and inconvenience, like stigmatization. In the current scenario, untreated obesity in childhood could lead to both.

'Benefit' must be considered at the level of the society as well as the individual, with the individual interest always taking precedence over the former. Here, the level of benefit is mainly determined by the adequacy of the information that is provided for obtaining consent. This is because, feedback, once results of the study do become available, considering the long duration of such studies and irreversibility setting in, may not actually make a difference. Though there may be a social benefit in terms of gain of knowledge, the individual who is a part of the study may not benefit, and when underinformed or misinformed may actually be harmed.

THERAPEUTIC MISINFORMATION

Another aspect, related to the two above, is the participants' perception that mere participation in a study is equivalent to receiving personalized medical care. This may lead to the participants receiving less than standard medical care. This again places a greater onus on the researcher to include the differences between a clinical study and clinical care in the informed consent. In the second example cited above, in some cases, it was found that, rather than being projected as an observational study, it was 'advertised' as 'an opportunity that is not to be missed'.

CONCLUSION

Prospective longitudinal studies in children pose numerous ethical questions, the answers to which are not in black and white, but in many shades of gray. Uniform guidelines across all population cannot resolve this ethical conundrum. Certain general principles tailored to each specific population and study is the need.

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