

## Ethical Considerations in Conducting Paediatric Research

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### Abstract

Health research is a moral duty because it is the foundation for evidence-based care by all health care practitioners. Hence, paediatric research is essential for improving health outcomes of children. Waiting for adult studies before conducting paediatric studies may prolong the denial of effective treatment for children. The CIOMS and other guidelines clearly allow research procedures that involve a low degree of risk. However, the critical need for pediatric research on drugs and biological products underscores the responsibility to ensure that children are enrolled in clinical research that is both scientifically necessary and ethically sound. Even in a resource poor setting of a developing country like Bangladesh, the things that should be taken under considerations are the status of children as a vulnerable population; the appropriate balance of risk and potential benefit in research; ethical considerations underlying study design, including clinical equipoise, placebo controls, and non-inferiority designs; the use of data; compensation; and parental permission and child assent where applicable to participate in research. Such ethical dilemmas are more evident in paediatric research especially when a collaborative research is done by a developed country in a developing country setting. It is the role of the health policy makers, and community of paediatric physicians, nurses, and caregivers to advocate not only for more research for children but also to ensure that the research conducted is of the highest quality from ethical viewpoint.

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### Introduction

Ethical considerations are integral to all health and biomedical research around the globe. Historically, research involving children has been discouraged on ethical grounds for decades, and essentially barred by the Nuremberg Code (1949).<sup>1-3</sup> However, there is a growing recognition of the ethical imperative to include children in research studies following recent evidence that paediatric research is truly beneficial, and an absence of such research can be harmful for innovation in paediatric treatment.<sup>4</sup> Besides, ethical reasoning in health research recognises that health research is a moral duty, because it is the foundation for evidence-based care by all healthcare practitioners.<sup>2,5</sup> Similarly, paediatric research or research in children is essential for improving health outcomes of children. Waiting for adult studies before conducting paediatric studies may prolong the denial of effective treatment for children.<sup>5,6</sup> However, while conducting paediatric research, there is always an obligation to adhere to ethical guidelines to

protect "the safety, human rights and cultural integrity of the children, their families and their communities".<sup>7</sup> The ethics of clinical research is based on several well-known guidelines and documents. The guidelines may also vary amongst countries;

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however, the principles of respect for persons, beneficence, and justice are constant. Some available universal guidelines are the Belmont Report (1979),<sup>8</sup> World Medical Association Declaration of Helsinki (as adopted by the 18<sup>th</sup> World Medical Assembly, Helsinki, 1964, as revised by the 48<sup>th</sup> World Medical Assembly, 1996),<sup>9</sup> the Council for International Organizations of Medical Sciences (CIOMS) (2002),<sup>1</sup> the International Conference on Harmonization - Good Clinical Practice guidelines (sometimes referred to as "ICH-GCP" or "E6", as of 1995).<sup>10</sup> However, this review paper will not provide an extensive list of all rules and regulations, or an in-depth discussion of all ethical issues, rather aims to outline some of the underlying principles of research ethics and highlight some important controversial areas particular focus on research involving children. It is expected that this review may help paediatric researchers in designing ethically sound studies by providing a better understanding of what ethics board/committee looks for after protocol submission.

### **Ethical Concerns in Research Involving Children:**

The core principles of ethical protection developed over ages are respect for persons (the recognition of the right of persons to exercise autonomy), beneficence (the minimization of risk incurred by research subjects and the maximization of benefits to them and to others), and justice in research studies and clinical trials (the principle that therapeutic investigations should not unduly involve persons from groups unlikely to benefit from subsequent applications).<sup>8,11</sup> The use of children in research raises the questions about proper justification of the research, assessment of benefits and risks, children's ability to consent, proper compensation, and justifiability of the selection of the research subjects.<sup>3,4,12-18</sup> Although substantive and procedural standards have evolved through decades, subpopulations of vulnerable children created new challenges and

concerns till date.<sup>4,14,18</sup> The first and foremost integral point of respect to individual is the consenting process. Part of practicing respect in research is ensuring that participants are fully informed. Clinical research professionals must ensure that the family has the information necessary to make the best decision for the child and the family. As 'written informed consent' is a necessity, the consent form should communicate the following in a clear and respectful manner: research timeframe; title of research; researchers involved; purpose of research; description of research; potential harms and benefits; treatment alternatives; statement of confidentiality; information and data to be collected; how long the data will be kept, how it will be stored and who can access it; any conflicts of interest; a statement of the participant's right to withdraw from participation at any point; declarative statement of understanding that the potential participant agrees to and signs.<sup>5,6,12-17</sup> The consent form should be in a language the potential participant understands (better to be in native language or in English with a translated copy). For potential participants with limited literacy, the verbal communication of the consent-document details should be provided along with proper documentation of consent, if it is given.<sup>12-18</sup> Besides, research investigator(s) should recognize that children are developing autonomous decision-making capacity.<sup>14-16</sup>

Researchers should be attentive to inclusion of children in the discussion of consent for research participation. Besides, when full consent is not possible, assent should be appropriately sought from children and dissent carefully considered.<sup>7,11,15-18</sup> As per clarification from WHO, assent is "a variation on consent where a person who does not possess full competence to give informed consent gives affirmative agreement to participate in research. For instance, a child or person with dementia should give assent before being enrolled in research. However, it is important to note that assent does not eliminate the need for obtaining the permission of a parent or other legally authorized

decision-maker".<sup>11</sup>

Participants must be protected from unnecessary harm by following all aspects of the protocol and having strong oversight by the clinical investigator. This should be a prime consideration that what will happen to participants who need medical attention during or after the study, either because they suffer injuries as a result of participation or because of the natural progression of a pre-existing illness.<sup>7,11,16,18-21</sup>

Sponsors' obligations to provide care in such circumstances should be clearly established before a study begins and made clear to potential participants during the consent process.<sup>11,19-22</sup> The use of placebo is often needed for scientific reasons, including pediatric trials. However, they are criticized because of the use of placebo controls. The most compelling reason to use a placebo-controlled study is that it provides definitive answers to questions about the safety and value of an intervention in the setting in which the study is performed and placebo-controlled study usually provides a faster answer to comparing drugs both in fewer subjects in a single-centre and larger population in multi-centre trials.<sup>16-18</sup>

However, it is to be noted that when an effective treatment already exists, it is unethical to create a placebo group that will receive no treatment.<sup>4,7,17,18</sup>

### Special Considerations in International Collaborative Research

Various representatives of the ministries of health, communities, and scientists in developing countries have joined with other scientists to call for less complex and less expensive interventions to counteract different health conditions and diseases.<sup>17,22-26</sup> In international collaborative research, review by a local research ethics committee may be required by the laws of the country in which the research is being sponsored, even if it is not required by the host country's own laws.<sup>11,22,26,27</sup> The committee represents the interests of the local population. It ensures that the

participants and their communities will receive fair benefits from the arrangement and prevent exploitation as well. In studies involving medical interventions, the committee must determine that adequate care and treatment will be provided for participants.<sup>11,21,23-25</sup> Moreover, the complexity of the notion of risk, as well as the uncertainty of the potential benefits of international research, make the process of risk/benefit assessment a significant challenge for all involved in the process. However, Risk/benefit assessment does not stop at the individual, rather it must also take into account communities and health systems of that country. The risks of research are not only limited to potential physical harms, but can also include psychological, social, legal and economic ramifications, as the socio-economic and cultural differences prevail between that developing country and its western counterpart.<sup>6,7,14,25-27</sup> Besides, an important point is evaluation of the benefits of research must distinguish between direct benefits for the individuals who participate in the study, expected benefits for the community in which the study will take place and potential benefits to science and the world at large.<sup>11,14,23-27</sup>

To summarize, in international collaborative research, the balance of access to current research and treatments must be weighed against risk for all involved.

### Research Ethics is Everyone's Responsibility:

The stewardship of ethical research is the responsibility of everyone involved, including principal and co-investigators, research associates, funding agencies, policy-makers and finally, the research ethics committees.<sup>11,18,21</sup> Consequently, there is a need for critical engagement by all stakeholders around some basic, but important, questions which are essentially ethical in nature and require close attention before the research makes its way advancing to any kind of ethics review committee (ERC).<sup>11,18,22,25</sup> For an example, "*Why is this research being conducted?*"

and "Who will be the beneficiaries of the research and how?" or "Do children necessarily need to be the participants/the population in the research or is there any other way that the information can be obtained?"; "What would be the possible consequences/demerits of not involving children?"- the importance of these kinds of questions gets more intensified when the research involves children and young people of the community.<sup>22-27</sup>

In certain jurisdictions, legislation established legal answers to those questions; however, ethical answers remain more elusive.<sup>18,21-27</sup> Researchers, care givers and others involved must choose either justice for one child or for children of the future, as ultimately there are no absolute or generic answers, only broad guidelines for case-by-case analysis.<sup>11,18,20</sup>

In Bangladesh, "Ethical Guidelines for Conducting Research Studies Involving Human Subjects" has been published recently by the Bangladesh Medical Research Council (BMRC), which is a national guideline that outlines special sections on vulnerable population like children.<sup>28</sup> International collaborative research can be done in any site of Bangladesh with permission of the national ethics committee of BMRC.<sup>29</sup>

We deeply feel the importance of developing a culture of solidarity and true partnership between developed and low-income country organizations, which will allow all those involved, and especially child patients, to benefit from the advancement of therapeutics. To summarize, the most essential principles behind are distributive justice in making high-quality health care available to all populations, including vulnerable ones like children, beneficence in providing evidence-based care to act on the best interest of the paediatric participants and non-maleficence in avoiding harmful therapies, adopted either without evidence or extrapolated from experience with adults. Finally, we believe that encouraging excellent, informative research in children supports those basic principles and will lead to improved child health in a society.

## Conclusion:

We tried to provide general pediatricians with a bird's eye view account of the process and regulatory framework on conducting research involving human participants to some extent. This review could not cover the myriad of issues and ethical views involved in paediatric research; however, the most crucial and frequent ones were discussed. It was intended to initiate ethical discussions that can motivate intellect of the respective professionals and continue to help them define their values to their own practice as well. It is the role of the health policy makers, and community of paediatric physicians, nurses, and caregivers to advocate not only for more research for children but also to ensure that the research conducted is of the highest quality from ethical viewpoint. Besides, international collaborative research should be monitored well to prevent exploitation and ensure maximum benefits.

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