CLINICAL INVESTIGATION

# Clinical trials in pediatrics

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**Keywords:** children • clinical trials • outcome measures

"Children are not little adults." Almost all aspects of children's health including clinical trials and drug development are poor cousins of adult health. Over the years, pediatricians worldwide caution against blind extrapolation of adult data to children as it may result in considerable harm [1,2]. Also, it is increasingly recognized that the roots of many chronic diseases in adulthood stem from childhood and tackling health issues in children lead to improved health in adults [3,4]. Furthermore, investment in early childhood has long-term benefits in adults not only in health but also in other aspects of life such as education and crime reduction [4,5]. Arguably, health at birth is the single most important predictor of health in adulthood as the inequality of an infant at birth has intergenerational effects [5]. The Carolina Abecedarian Project showed that early childhood programs that are of high quality result in substantial societal benefits (e.g., reduction of crime, increased earnings, better education) [4,5]. A recent publication from this project found that this benefit also translated into improved adult health outcomes [4]. In a randomized trial, Campbell and colleagues described that disadvantaged children who were randomized to the intervention group (early education, health screenings and nutrition program) had significantly lower rates of metabolic syndrome, obesity and hypertension, when aged in their mid-30s, compared with the control group [4].

In specific disease types, although patients may be diagnosed with the condition only later in life (i.e., in adulthood), many are symptomatic from childhood and those with earlier onset disease often fare worse [6]. For example, severe bronchiectasis in adulthood can be prevented by good clinical care in childhood before irreversible damage occurs [7]. In the respiratory system, the lung continues to grow at least till 7–8 years of age, if not longer; and the pulmonary immunity and respiratory phenotype is influenced by genetic–environmental interactions that commence very early in life (possibly *in utero*). There is indeed increasing evidence that a substantial proportion of lung disease in adults (e.g., chronic obstructive lung disease and bronchiectasis) has its roots in childhood (where it is potentially reversible) [8,9]. To reduce the world-wide burden of chronic respiratory illness, a greater focus on children's lung and generic health is required [3]. Many, if not most of these diseases, are potentially modifiable through clinically based interventions or are preventable.

Thus not surprisingly, pediatricians and clinical researchers repeatedly call for increased research relevant to improving the health of children. However, funding for pediatric studies falls well short of that for adults. In a study that reviewed data on pediatric and adult drug trials, Bourgeois and colleagues found that, "for the conditions selected, 59.9% of the disease burden was attributable to children, but only 12.0% (292/2440) of trials were pediatric ($p < 0.001$)" [10]. The authors tracked all drug trials within a 5-year period and also described that pediatric trials were more reliant on government and nonprofit organizations, compared with adult-based trials [10].

There are many differences between conducting studies in children compared

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with adults. These range from clinical end points to ethical issues. Examples of differences in relevant clinical end points are that used in the area of cough, the most common symptom in respiratory diseases. In adults, cough sensitivity is influenced by gender but in prepubertal children, age and not gender influences cough sensitivity [11]. The many ethical issues related to clinical studies in children include the manner by which consent is obtained from parents who act as proxies [12], and the possible for very long-term harm. Furthermore, trials in older children require not only parent consent but also assent from the child, yet there are inconsistencies between guidelines on how that should be obtained and how to determine capacity to consent [13]. These issues become increasingly complex in trials of drugs and vaccines in postmenarche females where pregnancy testing and/or contraception are required during the study.

The series of articles in this collection focus on various broad aspects of clinical trials relevant to children, ranging from legislation [14], methodological issues relevant to improving clinical trials [15,16] to disease-specific issues [17–19]. The issue of pediatric exclusiveness in clinical trials and financing drug development for children has been summarized by Hill and colleagues [20]. Auby [14] deliberated relevant legislation issues around pharmaceutical research in children. The important concept of the placebo effect in pediatric studies and its comparison to adults has been reviewed by Weimer and Enck [21] and that related to blood sampling in children discussed by Veal [22]. Needham and colleagues [16] highlight the initiative in Canada and a framework on improving the design, conduct and reporting of clinical trials in children. Pavuluri [23] uses bipolar disorder to provide an example of the challenges in conducting clinical trials in children. Weiss and Litonja [15] discusses methodological issues relating to clinical trials to prevent and/or treat childhood asthma in their paper, focusing on the concept of generalizability. Ways to improve the efficiency of early trials relevant to pediatric oncology were reviewed by Blanco and Hargrave [17]. Another article by Hill and colleagues [19] highlights the issues of clinically important end points relevant to antihypertension agents. Benz and colleagues [18] provide an overview of recent trials on the treatment of children with frequent relapsing syndrome.

This issue highlights some pediatric relevant clinical trials advances and brings clarity to some issues. Much more is required for the advancement of pediatric clinical trials so as to improve the health of children, particularly those in neglected areas relative to burden of disease such as parasitic infections in children. We also need to find ways where resource-rich countries conduct relevant research so as to find interventions that can be applied to resource poor settings. Given recent data consolidating the importance of early intervention in preventing disease and promoting health, [4,5] a paradigm shift in government policies that focuses on early childhood (as opposed to the heavy emphasis on adult care) is required.

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