Review Article

Necessity and limitations of paediatric research—a personal view

Rudolf Korinthenberg^

Research Ethics Committee, University of Freiburg, Freiburg, Germany

Correspondence to: Prof. Dr. Rudolf Korinthenberg. Research Ethics Committee, University of Freiburg, 79115 Freiburg, Germany. Email: rudolf.korinthenberg@uniklinik-freiburg.de.

Abstract: The objective of this review is to present a personal view on the need of paediatric research and its practical and ethical boundaries. The review is based on the personal experience of a senior paediatric neurologist and head of a research ethics committee, taking into account selected references. In summary, the physical and psychological immaturity and developmental potential of children, especially at a young age, require specific, age-appropriate research methods and topics that differ from research on adults. Worldwide, many children still die from common and treatable diseases such as measles and pneumonia. On the other hand, new lifestyle-dependent diseases such as allergies, attention deficit disorder and obesity are rapidly increasing in number in industrialised countries. With the gradual elucidation of the genetic causes of rare diseases, interest in their treatment is also increasing. The necessary research includes age-related physiological and pathophysiological, pharmacological, psychosocial, educational, epidemiological and socio-economic studies. However, young children are not able to understand complex instructions and follow study protocols, which makes it difficult to conduct reliable and valid studies. In addition, the rarity of many paediatric diseases and the different age groups often require national and supranational research groups with the associated high costs. As children have limited capacity to understand and consent to the risks and benefits of their participation, they are considered particularly vulnerable persons who need to be protected in all types of research in accordance with international ethical regulations and laws. In conclusion, as research on children tends to be more complex and less often refinanced, public and private sponsors, regulators and public health systems are called upon to support the necessary research on children in any way they can. This is not only about developing new therapies for rare diseases in developed countries, but also affordable therapies for common diseases in poorer regions of the world.

Keywords: Children; pediatric research; ethical regulations; new drugs; affordable drugs

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Introduction

Children are the future of our world and its most important resources. Therefore, their physical, cognitive and psychosocial health and education are of utmost importance. However, their number and their share in the population are very unevenly distributed. While the proportion of people under 20 years of age in highly-developed countries has steadily declined to about 20% in recent decades, the young age groups make up the largest part of the population in economically less developed regions. Infant mortality is considered one of the most important parameters for the quality of health care. In Germany, as in other highly developed countries, it has fallen from 185 to 3–4/1,000 live births in the last century. In regions such as Central Africa and Asia, however, it is still much higher (50–100/1,000 depending on the country). Child health and survival have improved through advances in general hygiene, nutrition, immunisation, antibiotics,

^ ORCID: 0000-0002-4638-3460.

neonatal care, rehydration and other emergency therapies. However, large numbers of children under the age of five still die worldwide from pneumonia, diarrhoea, malaria, measles and the consequences of premature birth and perinatal complications because effective treatments are still not available in developing countries (1). So, there is clearly still a great need for paediatric research that addresses both the development of age-appropriate medicines and the organisation of the health system to improve children's well-being. The aim of this review article is to present the author's personal opinion on the necessity and limitations of research for and with children.

The necessity of research for children

Children should not simply be regarded as small adults. Their organ systems are still developing and react differently to disorders than adults; this may result in a better or worse recovery than in an adult, depending on the stage of development of the organ and the nature and extent of the damage.

When we speak of "children", we need to be aware that we are dealing with age groups ranging from early preterm birth to adolescence, and that the physiological differences between preterm and newborn infants compared to adults are much greater than those between school children and adults. Addressing the period from prematurity to late infancy, there are major physiological differences far beyond the differences in body weight and different normal ranges for laboratory tests. Among them belong a different body composition with a much higher water content, a different digestive and absorptive capacity of the gastro-intestinal tract and first-pass effect in the portocaval circulation, different binding capacities of serum-proteins, an immature function of de-toxifying enzyme systems of the liver and a different excretory function of the kidneys. Ignorance of these conditions in the past has led to complications such as the severe Grey syndrome (chloramphenicol toxicity in prematures) or neonatal Kernicterus with lipid-soluble drugs such as benzodiazepines (2). Of course, the situation is not that critical in all age groups; a combined review of clinical trials with new antiepileptic drugs including adults and 12–<18-year-old patients showed that there were no significant differences both regarding efficacy and tolerability of the treatment (3).

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is an association of regulatory authorities and the pharmaceutical industry from Europe, the USA and Japan. Its aim is to develop common guidelines for the evaluation of the quality, efficacy and safety of medicinal products. In their guideline ICH E11 on clinical trials of medicines in the pediatric population, they stated that there is a high need for clinical trials in children to address the lack of medicines with well-documented efficacy and tolerability data in the youngest age groups (4). Traditionally, for many diseases and treatment situations, the dosage of medicines is calculated down from the approved adult dosage based on relative body weight or body surface area. Paediatricians know that this is not appropriate, but often do so because of a lack of medicines that are appropriately studied and licensed for children. It has been reported that up to 50% of children hospitalised in pediatric wards and 90% in neonatal intensive care units are treated with medicines not approved for children, while this figure is lower in primary care (5).

However, the necessity of research for separated age groups does not only apply to pharmacological research, but also to studies in basal physiological and pathophysiological mechanisms of diseases specific for that age. Among others this could address intraventricular hemorrhage in prematures, hypoxic-ischemic brain damage in neonates and older ages, age-specific infections and their complications such as multisystem inflammatory syndrome in COVID-19, or endocrinological changes associated with puberty, obesity and metabolic syndrome. While in large parts of the world children still suffer and die from old and treatable diseases, in economically high-developed countries new, age specific chronic disorders arise and consume a considerable part of pediatrician's interest and time. For young children this comprises obesity, asthma, suboptimal motor coordination, attention deficit disorder and conduct disorders, and for older ages drug abuse (including abusive consumption of internet games), eating disorders and sexual disorders. Therefore, there is a great need for research in the field of cognitive, educational and psychosocial development, which will not be discussed in detail here. This research has not only the aim to elucidate the physiological and pathophysiological basis, but also to develop and implement effective and cost-efficient programs for prophylaxis and treatment (6-8).

The frequent and increasing diseases are not only a burden for the patient himself and his family, but also for society and the public health system. The increasingly diagnosable rare diseases, which are mostly of genetic

origin, are also a burden primarily on families, but also on the health system due to the high costs associated with them. In all cases, research on health care and health economics is urgently needed to increase medical and economic efficiency.

Practical limitations

Some practical limitations make clinical research in the very young age groups difficult or even impossible. While for an experienced pediatrician the clinical investigation of small organs and puncture of tiny blood vessels or cerebrospinal fluid (CSF) spaces is more an ethical than a practical problem, the inability of the child to keep still in a frightening situation frequently requires a deep sedation or even general anesthesia which depending on the expected benefit for the child can be an ethical "no-go". Functional testing which is an important part of neurological and psychological clinical research requires the child's basic understanding of the task and the ability and readiness to cooperate. Automatic reflexes and more complex reactions (such as the Moro, ATNR, glabella, handgrip and Galant reaction) can reproducibly be examined already in newborns. However, the further classical neurological examination must be replaced at this age and far into infancy by standardized observations of posture and behavior (such as the Dubowitz scale and Prechtl's General Movement evaluation). In addition, a sensory stimulation can add to the findings, starting with the Brazzelton Neonatal Behavior Scale and comprising different elaborated methods of visual and auditory stimulation in part involving apparated measurements (evoked potentials, oto-acoustic emissions). In the second and third year of life children are increasingly able to follow simple instructions, which form the basis of the multiple tests of child development at hand (for example the Bayley III test which is validated for multiple ethnic populations). From the age of 4 or 5 years onward cooperative preschoolers can be investigated with more complex instructions to test strength, gross and fine motor-coordination, changes of position, walking, respiratory function and more. In addition, formal IQ- and neuropsychological testing is possible from 4–6 years onward with appropriate test materials.

Beyond the age and physiological inability to cooperate one has to consider the disease process, which is the objective of the research. Even in older children with significant impairments such as cerebral palsy, Duchenne muscular dystrophy or severe heart failure, many standardised and validated tests cannot be used reliably because the child is unable to perform the required tasks. Children both with static and progressive neurological and developmental diseases show very individual developmental trajectories, which contribute to the variability of the outcome measures and make planning of a clinical trial difficult. For example, in a group of 5–7 years old boys with Duchenne muscular dystrophy some may still show spontaneous functional improvement, while others have entered the "plateau-phase" without further gain of function, or they have already entered the phase of motor decline when they can rapidly lose the ability to walk. So while "walking ability" is a very reasonable functional outcome measure for the growing number of clinical trials on this disease, it has proven extremely difficult to validly measure walking ability in terms of quantity and quality and to define the age group of patients to be included.

A major obstacle to research on children is the fact that children get sick less often than adults after the neonatal period, apart from the usual everyday infections and accidents. Thus, it may be difficult to recruit a sufficient number of patients for a statistically well-powered trial. This is especially true for the rare but very severe hereditary diseases, for which treatment with new drugs or gene therapies is increasingly being tested in clinical trials. These are usually only feasible in a multicenter and usually multinational approach. A further obstacle can be the lack of readiness of the parents to let their child take part in a research project. For some of the families it is difficult to accept a randomization of treatment arms, even in a study with an active comparator. For many of them the multiple, regular visits in the study center are a severe burden, especially when they have to travel long distances and both parents have an occupation. And a third problem is that as soon as a new drug has got a marketing authorization for adults, physicians can prescribe this off-label for children; so, the parents see no necessity to enroll in a burdensome clinical trial to get access to this drug.

Ethical and legal limitations

The primary objective of clinical research is the improvement of our knowledge in health and disease, and not the individual treatment of the participating patient. Nevertheless, the participants could gain an individual benefit, but in randomised studies, we can never predict this. Further classes of benefit from a study are the "group benefit" in later patients with the same disease and treatment

requirement, and the "societal benefit" of an increased knowledge in etiology, pathophysiology, natural history and treatment of a disease. As always in decisions about medical interventions, also in medical research we have to weigh the possible benefits of an intervention against its risks and burden. And even more than in clinical practice, the patient must be fully informed about the background and aims of a study and its methods and associated benefits and risks. The researcher must inform the potential participants in a study in such a comprehensive and comprehensible way that they are able to make their own decisions, weighing their individual potential benefits against the risks and burdens of their participation. The World Medical Association (WMA) has fixed these and other aspects of the ethical principles of research with humans, their biomaterial and their identifiable data in their Declaration of Helsinki: ethical principles for medical research involving human subjects (9).

Due to their young age, stage of development and dependency, children are not or only to a limited extent able to understand the background, risks and benefits of a study and to make a balanced decision. Furthermore, they are physically and mentally relatively weak and hardly able to resist the decisions of their doctors and caregivers. So, in the context of research they are regarded a vulnerable group that needs special precautions and protection before entering and when undergoing a scientific project. Until 2013 the Helsinki Declaration excluded all vulnerable persons from research that could not be expected to obtain an individual benefit from their participation—thus, among others clinical trials with a placebo control group in children were not accepted. However, in its most recent version from 2013, the Helsinki Declaration included a group benefit as justification for research in vulnerable groups "if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research (§20)", and "the physician must seek informed consent from the legally authorized representative. …, and the research entails only minimal risk and minimal burden (§28)" (9).

The international regulatory and legal authorities now hold the same view. For clinical drug trials, this is documented in short form in the ICH guideline for Good Clinical Practice (ICH E6, GCP) (10). The European Union regulation 536/14 on clinical trials on medicinal products for human use (11) details the justifying conditions of clinical trials for children ("minors") in article 32 as follows (wording changed slightly by the author):

A clinical trial on minors may be conducted only when all of the following conditions are met:

(I) the informed consent of their legally designated representative has been obtained;
(II) also, the minors themselves have received the information about the trial in a way adapted to their age and mental maturity, and from members of the investigating team who are experienced in working with children;
(III) the explicit wish of a minor who is capable of forming an informed opinion to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator;
(IV) no incentives or financial inducements are given to the subject or his legally designated representative except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial;
(V) the clinical trial is intended to investigate treatments for a medical condition that only occurs in minors, or the clinical trial is essential with respect to minors to validate data obtained earlier in clinical trials in persons able to consent;
(VI) the clinical trial either relates directly to a medical condition from which the participating minor suffers or is of such a nature that it can only be carried out on minors;
(VII) there are scientific grounds for expecting that participation in the clinical trial will produce:
    (i) a direct benefit for the participating minor outweighing the risks and burdens;
    (ii) some benefit for the population represented by the minor and such a clinical trial will impose only minimal risk to, and minimal burden on the minor in comparison with the standard treatment of the minor's condition.

In practice, this means that in studies with children, the patients themselves must be informed about the study in a way that they can understand: in the case of preschool children, usually orally, and from school age onwards, in writing in age-appropriate language. In studies without individual benefit, interventions must be limited to those with only low burden and risk (e.g., MRI at most with sedation and without general anaesthesia, no repeated biopsies and lumbar punctures, blood quantities for laboratory tests limited to the maximum usual for the age of the patient). The rationale for these regulations and age-

appropriate details are explained in the following text that I can recommend for further reading: "ethical considerations for clinical trials on medicinal products conducted with minors" (12).

Although the above criteria are only legally required for drug studies, they should also be used in an adapted form as ethical guidelines for all other types of studies on children and adolescents, from basic pathophysiological studies to epidemiological research.

Economical limitations

Resulting from progress in pediatric research and child health, during the second half of the 20th century the epidemiology of diseases in childhood in developed countries has changed significantly from acute infections (gastro-enteritis, pneumonia, meningitis) to chronic diseases (allergy, asthma, diabetes mellitus, obesity) and developmental problems (attention deficit disorder, autism, residua of perinatal conditions). As a result, patient care has undergone a major shift from acute inpatient to chronic outpatient care, and the number and size of children's hospitals has declined significantly. In Germany, even the third-level and university pediatric hospitals have rarely more than 150 beds. This coincides with an increasing specialization also in pediatrics. Especially in university hospitals, specialists in infectiology, neurology, oncology, cardiology and multiple other disciplines are struggling for staff and economic resources.

In this situation, valid research projects giving rise to high-evidence level knowledge cannot be performed by house staff alone, but it needs third party funding by public funding bodies or pharmaceutical companies and medical device manufacturers. This funding includes treatment cost for the participating child and overhead cost for the institution in which the research takes place. However, due to the rarity of diseases, the multiple dosages and formulations that have to be approved and the complicated trial regulations for different pediatric age groups the refinancing of pediatric drug development is difficult for pharmaceutical companies. The European Medicines Agency (EMA) and other regulatory authorities addressed this situation in 2001 in their note to guidance CPMP/ICH/2711/99 [2]. Since 2008 a pharmaceutical company applying for a marketing authorization for a new drug in adults has simultaneously to present a pediatric investigation plan (PIP) describing their concepts for clinical trials also in the pediatric age-group. They only can apply for deferral of this obligation when the new drug is not expected to play any role for children in the future. For drugs that are already licensed for adults, they can apply for a pediatric use marketing authorization (PUMA) that is also based on appropriate age-specific clinical trials. In return, companies can obtain an extension of the product protection for the adult authorization (4).

Due to these new regulations for drug development in children, the number of pediatric drug trials is slowly increasing. But there is yet another political incentive that has in recent years increased the interest of pharmaceutical industry in developing medicines for rare diseases in children. The regulatory authorities' orphan regulation since 2017 has facilitated the regulatory process of drug development for rare diseases (prevalence <2,000 persons) that have received a designation as orphan drugs (13). As in oncology, the discovery of the genetic background of rare diseases and their pathophysiological pathways has opened the possibility to develop targeted and individualized therapies for a rapidly increasing number of pediatric diseases. The actual therapies comprise gene therapies, gene modulating methods (such as antisense-oligonucleotides) and monoclonal antibodies or small molecules that interfere with pathway function. Usually, the basic idea for such a treatment is developed with public funding in research institutes, preclinical and early clinical development is carried out by scientific start-ups with private funding, and the subsequent large-scale registration trials are financed by large pharmaceutical companies and brought to market. Since in this type of drug development the costs cannot be refinanced by a high number of drugs sold, the sales price for these medicines after market approval is extremely high. For example, the price of the "one-shot" gene therapy onasemnogene abeparvovec (Zolgensma®, Novartis/AveXis, Switzerland) for young children with spinal muscular atrophy is almost €2 million; this makes it the most expensive drug on the market today. This development leads to new economic constraints. It is obvious that patients and families are not able to pay such high amounts themselves. But which health insurance fund or public health system is able and willing to bear such high costs, and is this fair from an international perspective? There is a threat of a new inequality in the treatment of these patients, not only between developed and less developed countries, but also within a country, depending on the insurance system and socio-economic status of the family. So, the

progress in pediatric research that many patients, families and clinical researchers have longed for is leading us to new serious ethical problems. And this development in no way contributes to providing the large number of children in developing countries with affordable medicines for their everyday illnesses (14).

Conclusions

Children are a very important part of the world's population. Their immaturity and developmental potential require specific, age-appropriate research that differs from research conducted on adults. In the 20th century, children were rarely allowed to be included in randomised clinical trials, which more or less excluded them from medical progress. In medicine, every innovation carries a certain risk of harming the patient. Especially in research with children, it must be ensured that this risk is outweighed by the expected benefit of the innovation for the individual or the group. As children develop, long-term follow-up studies are imperative to identify developmental side effects of the intervention. Because research on children is typically more complex and rarely refinanced, public and private sponsors, regulators and public health systems are called upon to support necessary research for children. And even in studies with negative results, researchers are encouraged to publish all their data to avoid unnecessary duplication of effort with exposure of even more children. In our increasingly economized health systems, researchers and ethics committees must also consider the economic risks and benefits of innovation. And from an international perspective, efforts should be made to develop not only effective but expensive therapies, but also equally effective but less expensive interventions for the less affluent regions of the world.

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Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm-21-90/coif). The author declares participation in a data safety monitoring board (University of Basel/Switzerland). The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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