Chapter 25
Clinical Testing in Children

Klaus Rose

Abstract Clinical trials systematically compare safety and efficacy of different therapeutic interventions. Since the 1960s proof of efficacy and safety through appropriate clinical trials are a legal requirement for the registration of drugs, and that made the advent of drug labels in the modern sense of the word. Regulatory clinical trials have become one cornerstone of the drug development process. Pivotal trials are decisive for registration: a drug may show promising results in early trials; if it fails in the pivotal trials, it is abandoned—or developed for another indication. In parallel to industry-sponsored clinical trials with regulatory purposes, academic trials continued. They aim at improving interventions without regulatory concerns. When modern labels were introduced, children were largely excluded from regulatory clinical trials. With increasing understanding of the child's developing body and how it interacts with drugs, i.e., with the evolvement of pediatric clinical pharmacology, dosing based on mechanical formulas was understood to be insufficient. Pediatricians used the increasing number of available, highly effective, adult drugs off-label also in children, but a gap was perceived between the attention given to adults as compared to children. The child version of the British National Formulary (BNF) was a pragmatic attempt for reconciliation. Pediatric oncologists developed new off-label treatment schemes for adult anticancer drugs—also a pragmatic approach. Since 1997, US pediatric legislation encourages pharmaceutical companies to generate additional pediatric data. The 2006 EU pediatric legislation aims at investigating the potential pediatric use of new drugs already during early drug development and at their registration in children. In short, we have at least four developments: (1) a better understanding of the child's developing body and how it impacts drug treatment; (2) the expansion of the framework and the science of human clinical trials into addressing child-specific aspects; (3) facilitation of

K. Rose (✉)
klausrose Consulting, Pediatric Drug Development and More,
Aeussere Baselstrasse 308, Riehen 4125, Switzerland
e-mail: klaus.rose@klausrose.net

D. Bar-Shalom and K. Rose (eds.), *Pediatric Formulations: A Roadmap*, AAPS Advances in the Pharmaceutical Sciences Series 11, DOI 10.1007/978-1-4899-8011-3_25,

generating additional pediatric data by US legislation; (4) EU's wish to use pharmaceutical industry's financial and research potential for the benefit of children. Both US and EU legislation request age-adapted pediatric formulations.

25.1 Clinical Trials in Man

Clinical trials assess *and compare healthcare interventions, mostly drugs, diagnostics, vaccines, and medical* devices. Historically, treatment of patients was based on empiricism and anecdotal reports on the efficacy of interventions. Ancient surgeons learned from individual masters, and improvement was by trial and error. However, in the long term anecdotal reports alone are insufficient. Clinical trials minimize as much as possible the variables that could be confounders and apply the intervention of interest side by side to another intervention (or lack thereof) that serves as control. One of the most important features of a clinical trial is the identification a priori of endpoints. The endpoints are the desirable outcomes of the interventions at play [1].

In a study described in 1753 by James Lind in his book, "A Treatise of the Scurvy," he divided 12 scorbutic sailors into 6 groups of 2. All received the standard diet but, in addition, group one was given a quart of cider daily, group two received 25 drops of vitriol (sulfuric acid), group three received six spoonfuls of vinegar, group four received a pint of seawater, group five received two oranges and one lemon (citrus fruit), and the last group received a spicy paste plus a drink of barley water. The citrus fruit treatment stopped early when they ran out of fruit, but by that time one sailor was fit for duty and the other had almost recovered. Apart from citrus fruits, only cider showed some treatment effect. By today's standards, the trial had several serious flaws, including non-adherence to the protocol due to logistical deficiencies. The basic approach, however, i.e., the systematic and open-minded comparison of different treatments, was in line with modern testing. For various reasons, the findings from this trial did not translate immediately into action in the royal navy [2–4].

Systematic testing was and is part of the scientific and technical revolution. Testing in man has become more frequent with the availability of standardized drugs, devices, diagnostics, and scientific publications. During and after World War II, medical research expanded at an extraordinary rate [5]. After 1945 the world was outraged by the murders conducted in humans in general and specifically in children by Nazi physicians such as Josef Mengele and by Japanese physicians in occupied China [6, 7]. The judges in the trial against Nazi medical doctors in Nuremberg, Germany, published in 1947 a list of principles that became the "Nuremberg Code." This code promulgated key issues of human experimentation [8]. The outrage after World War II did not lead to the application of the newly pronounced Nuremberg Code to experimentation in man in the USA [9].

In 1964, the Declaration of Helsinki (DoH) was adopted by the World Medical Association (WMA) as a set of ethical principles for the medical community regarding clinical research in man; children are not mentioned in any version of the DOH, but are part of the mentioned research subjects that are "legally incompetent" [10].

In 1966 the US American Harvard anesthesiologist Henry K. Beecher summarized 22 selected academic research projects that had been published in academic research journals that were unethical by contemporary ethical standards. One example was infection of mentally retarded children with hepatitis [5]. These were academic trials. Beecher's explanation of the reason for the massive increase of clinical research was the increased availability of government funds. Since then the funds available for clinical research have continued to grow, and so the basic challenge has continued to exist: hidden interests of the sponsor vs. the interests of the study participant. In the beginning of large-scale clinical trials in post-World War II North America were often performed in young male adult prisoners, and included the testing of toothpaste, deodorants, shampoo, skin creams, detergents, liquid diets, eye drops, foot powders, and hair dye [6, 11].

Two major types of clinical trials are still frequently differentiated: academic ("investigator-initiated") clinical trials that compare different interventions or a new concept with standard treatment; the major aim of these trials is the creation of scientific publications that are the key factor in career progress of academics. The other trial type is in the framework of the development of drugs, diagnostics, vaccines, or medical devices. The key difference is that the latter aims at the registration of a product, so the study design must either have the pre-trial imprimatur of the regulatory authority or must follow official regulatory guidance [12]. There is still broad conviction that research initiated by academia is noble by character while research organized with the aim of commercialization is less noble. This belief is much stronger in Europe than in North America.

For both types of clinical research the same ethical and legal framework developed in the last century to balance society's interest to learn and the need to protect study participants. The key features are the study subject's voluntary participation, his right to terminate study participation whenever he wants, the need to fully inform the patient about potential benefits and risks, and the requirement to document this informed consent in writing, and an acceptable benefit-risk-ratio. All these features are codified in the rules of good clinical practice (GCP) [1].

25.2 Modern Drug Labels, Pediatric Disclaimers, and Pediatric Clinical Pharmacology

With the industrial revolution began the chemical production of drugs on a large scale in the nineteenth and twentieth century [13]. Modern medicines have a potential dual effect: their therapeutic potential is often enormous, see the immediate lifesaving effects of antibiotics, and often they also have the potential for harm. In 1936, a liquid formulation of sulfanilamide, an antibiotic, was brought to the market in the USA. The used solvent had not passed any safety testing—this was not required in 1936. Within days after introduction deaths were reported to the FDA. FDA seized the entire production lot. More than 100 patients died in this catastrophe. The public outcry lead to a serious revision of the FDA legislation,

mandating for the first time safety experiments in animals before a drug could be brought to the market [14]. In 1961/1962 a second major global catastrophe occurred when it became apparent that the sleeping pill thalidomide caused deformation in unborn babies when taken by pregnant women. Thousands of children were born with shortened and deformed arms and legs. With a few exceptions, these children were born outside of the USA, as thalidomide had not been licensed there. "Only" a few children were born with defects in the USA due to the generous and not controlled distribution of thalidomide tablets by medical doctors within so-called clinical trials that lacked even minimal documentation [13, 15]. Today, GCP requires a precise documentation of each single tablet and an emergency call-back of medication in case a safety issue is identified. The thalidomide catastrophe led to the US Kefauver-Harris amendments in 1962 that mandated drug manufacturers to perform adequate clinical trials to proof safety and efficacy of drug covering the claims of the respective drug in the drug label [16].

With the increased role of regulatory authorities their influence on drug development has increased considerably. Most clinical trials organized for commercial purposes are regulatory trials, i.e., trials that intend to back a marketing authorization application (MAA) in the EU or a submission in North America, Japan, or the rest of the world. Often the development budget of medium or large drug company exceeds by far the research budget of an academic institution or network. The costs of drug development have increased considerably. The development costs of a new drug today are estimated to be around US$1 billion. Within these costs, research, preclinical safety, and formulation development are comparatively low compared to the enormous costs of large phase 3 clinical trials.

Until the 1990s most pharmaceutical companies performed their clinical trials in-house. Since then, they are increasingly outsourced to clinical research organizations (CROs) that offer services from strategic development advice to protocol design and execution of the respective study including selection of adequate trial centers, organizing investigator meetings, coordinate patient recruitment, and offer support for electronic data capturing. The execution of clinical trials has become a business in its own right and looking at the enormous costs of clinical trial, it can also be described as a whole industry of its own [17, 18].

Regulation on drug development and modern labels initiated as national processes. For example, the Kefauver-Harris amendments were a national USA legal initiative [16], which was then followed by legal action by most other industrialized states. Today this had led to an international framework for drug development, the "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)". It was founded in 1990 to respond to the increasingly global face of drug development and to the need of international harmonization [19]. The title itself shows how difficult it is to get very different partners on one table and to agree at least on a common name. These partners are the trade unions of pharmaceutical industry in the USA (PhRMA) [20], Europe (EFPIA) [21], Japan (JPMA) [22], worldwide (IFPMA) [23] and the regulatory authorities of USA (FDA) [24], EU (EMA) [25], and Japan (MHLW) [26], with other regulatory authorities as observers. Both sides use academic specialists for specific issues.

The specific framework for clinical trials is documented in the ICH guideline ICH E6 on "GCP" [1]. Finalized in 1996, it summarizes the rules how clinical trials should be performed to meet the requirements so that the generated data are usable for registration purposes. It lists the responsibilities of the institutional review board (IRB)/ethics committee that must approve any trial, the responsibilities of the clinical investigator and his institution, the responsibilities of the sponsor of the trial including the logistics of the trial, the requirements for the study protocol, the investigator's brochure, and for other essential documents for the clinical trial. Of course, these principles must also be adhered to in clinical trials in children.

25.3 Pediatric Medicine and Clinical Trials in Children

Pediatrics is a rather young academic discipline compared to the history of other medical sub-specialties [27]. Looking through the development of pediatric medicine over the past century we see that the focus of attention shifted continuously with the mainstream of innovation and advances in learning. "Safe Milk Campaigns" to pasteurize milk, or the application of silver nitrate in newborns eyes to prevent blindness are today almost forgotten, as are the pediatric wards full of iron lungs, keeping children with polio alive during the 1950s. Children in modern society enjoy the best medical care that has ever been available in history, and children have certainly fully participated from medical progress over the past century, see, e.g., the advances in vaccination, in surgery of inborn heart failures, in child transplant medicine, and many more fields. Nevertheless, we observe today a new focus on improvement of drug treatment of children, which reflects further advances not only in pediatrics but also in the methodology of clinical research, and of a number of related scientific fields.

In reaction to the Kefauver-Harris amendments pharmaceutical manufacturers introduced pediatric disclaimers to document that the respective drug had not been tested in children. They did that to prevent being sued in case of adverse events. This left the medical doctor in the dilemma of either prescribing a drug he assumed to be effective and not prescribing the drug and withhold a potentially effective treatment. The potential legal liability shifted to the prescribing doctor and away from the manufacturer [28, 29].

In parallel to the increasing availability of modern drugs clinical pharmacology evolved as a new discipline, investigating absorption, distribution, metabolism, and excretion (ADME) of drugs [30]. As a sub-specialty pediatric clinical pharmacology evolved, initially as an academic movement [31]. The child's body is in many aspects not just a small adult body. In younger children the organs are not yet mature, and the liver, kidney, and other organs work differently from adults. Key learnings were summarized by the publication of Kearns 2003 [32]. The key message of pediatric clinical pharmacology is that due to the different organ systems dosing in children cannot be deduced mechanistically from the weight or body surface of children, specifically the very young. The consequence of this difference is that

by using mechanistic formulas and tables only (almost each EU country had a different pediatric formula) there is always a risk of over- or under-dosing, i.e., a given a dose has no clinical effect, or is toxic to the child. While in adolescents usually the adult dose is OK, systematic testing is specifically important in young and very young children.

There are also occasional observations made by clinicians that drugs approved for a given indication in adults can work in a completely different disease in children. Famous examples are indomethacin and ibuprofen, non-steroidal antiinflammatory drugs that show efficacy in closing the arterial duct, a vessel that in the unborn child connects the pulmonary artery with the aorta. Normally this vessel closes at birth. If it remains open, it can lead to pulmonary hypertension and impair the child's development [33].

The ICH guideline E11 "Clinical Investigation of Medicinal Products in the Pediatric Population" was finalized and adopted by FDA, EMA, and MHLW in 2000. In contrast to the rather technical title the objective is much broader: "The guidance provides an outline of critical issues in pediatric drug development and approaches to the safe, efficient, and ethical study of medicinal products in the pediatric population" (1.1, Objectives of the Guideline). It addresses pediatric formulations, time of pediatric development, types of drugs (for lifesaving in children only; lifesaving both in adults and children; all other drugs), age classification of children, and ethical issues in pediatric clinical research, and a number of technical issues such as withdrawal of blood. ICH E11 is a high level key document that everybody who wants to work in pediatric drug development should be familiar with [34].

25.4 US and EU Pediatric Pharmaceutical Legislation

Pediatricians, pediatric clinical pharmacologists, and regulatory authorities worked together in the US to address the problem of pediatric disclaimers and the fact that many modern medicines were not registered in children [35].

In 1997 BPCA (best pharmaceuticals for children act) [36] within FDAMA (FDA modernization act) offered for the first time a voluntary reward to pharmaceutical industry of a 6-month market exclusivity extension for the generation of pediatric data. The technical term for this patent extension is "pediatric exclusivity." BPCA was later complemented by the pediatric research equity act (PREA) [37], which gave the FDA the authority to mandate clinical trials and other measures to better consider children's treatment in the overall drug development. Both BPCA and PREA were re-authorized several times and became permanent law in 2012 [38].

The EU pediatric legislation came into force in 2007 [39]. It parallels the US legislation, but is much more ambitious. MAAs for new drugs must be submitted with a Paediatric Investigation Plan (PIP) approved by the European Medicines Agency (EMA) Paediatric Committee (PDCO), unless the EMA confirms in writing the applicability of a class waiver. Generic drugs are exempt, orphan drugs are not. Although it is the EMA CHMP (Committee for Medicinal Products for Human Use) that decides the approval of new drugs, the PDCO can block a submission. EMA will

not validate a submission without an approved PIP. The PDCO is composed of 33 members plus another 33 alternates. Each member state is represented by two: one member and one alternate; additional members represent CHMP, pediatric healthcare professionals, and patient advocacy groups. The PDCO decides about PIPs, waivers (no development in children), partial waiver (no development in specific age groups), and deferrals (later performing of studies).

The PIP must cover all age groups as defined by ICH E11: preterm newborns (<36 weeks gestational age), newborns (0–27 days), infants and toddlers (28 days to 23 months), children (2–11 years), and adolescents (12–17 years) [9]. The applicant should submit it at the end of human pharmacokinetics (PK), which EMA sees as the end of phase 1, i.e., before proof of concept. The PIP includes chapters on preclinical testing, including juvenile animal studies; formulation(s), e.g., intravenous for preterm newborns, liquids for infants and young children; clinical pharmacology for dosing; and clinical trials. To what degree it makes sense to ask for a detailed pediatric investigation plan at a development stage where more than half of the drug candidates will never reach phase 3 is a discussion beyond the scope of this book. Reference is made to other publications [40–42]. For developers of pediatric formulations the key message is that legislation in both the USA and Europe is increasing the demand for the development of more age-adjusted formulations.

25.5 Barriers Against Clinical Trials in Children

Why were there less clinical trials in children in the past? Well, there were many pediatric clinical trials in the past. Many of the 22 studies listed 1966 by Beecher were performed in children. The discussion today about inclusion of children into the pharmaceutical progress is predominantly aimed at the commercial drug development that on one side has without doubt been quite successful, on the other side has successfully managed to give the pharmaceutical industry a public image comparable to that of the tobacco industry.

There is a broad area of therapeutic indications where extensive pediatric research has been done in the past without additional pediatric legislation. For many decades, vaccine studies have been mostly performed in children. The same holds true for antibiotics, although the registration of an antibiotic for pediatric use is per se not always in the interest of children—many cases of otitis media are treated with antibiotics, but most of these treatments are unnecessary [43, 44]. Growth hormone was developed before the EU pediatric drug legislation. Where children represent a market on their own, they attract business. We see this with special shops for children's clothes, children's toys, children's push chairs, children's education, and so on [45]. Parents are prepared to spend a lot of money for their children. With drugs it is slightly different as usually parents do not pay directly but through a reimbursement institution. These institutions have many other clients to take care of as well. In consequence, they will go for the best price. There is no other population group that is that often treated with generic medication.

In the public opinion, participation of children in clinical trials has been perceived in the past in an ambivalent way. There is general agreement that children should not be abused as "guinea pigs" in clinical research. On the other side, probably nobody on this planet would object against treating children with cancer in the best way known to the medical community. Virtually all children with cancer in the developed world are treated routinely in the framework of clinical trials. The advances of pediatric cancer therapy resulted, e.g., in about 90 % of children with acute lymphatic leukemia to survive, a survival rate adult oncology could only dream about. Child oncology started in the last century with the systematic experimental use of cytostatic agents that had been developed for adult cancer treatment in the 1950s and 1960s. While initially mostly homeopathic, i.e., very low doses were prescribed, increased experience lead to treatment protocols that increased survival by about 10 % with the year of diagnosis since the 1970s. This was achieved by higher dosing and new combination of different drugs and treatment modalities. However, there is at present little progress to be expected from further increasing toxicity in pediatric drug treatment [46]. Instead, the pediatric oncology community is hoping for the development of new compounds better suited to treat childhood cancer [47]. Where the child's life is at stake and no well-established treatment is available, few parents hesitate to have their child treated within a clinical trial. Interestingly, most drugs used on a daily base in pediatric cancer treatment are not licensed for this treatment, as most used drugs are in clinical use since decades and are no longer patent protected. They were developed and licensed for adult cancer types and in most cases there is no incentive to register them for pediatric indications.

The present EU and US legislation ensure that new drugs will have an earlier age-appropriate formulation. This is specifically important for the very young. Most children under 7 years of age cannot swallow tablets, and for preterm newborns often special intravenous formulations are required.

This leaves three large areas open.

Firstly, as long as drugs are developed mainly for marketing reasons, the developers will aim at diseases where they have a chance to retrieve their original investments. At present, these are predominantly adult diseases. Some adult diseases exist in rare cases also in children, e.g., some types of cancer, or neurodegenerative diseases that can show first signs already in the second decade of life.

Secondly, there are many rare diseases in children that so far could not be treated successfully. Here modern technology carries some hope. First enzyme deficiency diseases can today successfully be treated with enzyme replacement therapy. In the last years, rare diseases have been discovered by research-based pharmaceutical industry as a new hot spot for drug development, predominantly as the old mass marketing model is increasingly abandoned. For many frequent diseases there are already enough generic medications available so the development of, e.g., yet another antihypertensive family of drug is more difficult to justify towards the reimbursement institutions than it used to be decades ago.

Thirdly, there are many old medications that are no longer patent protected. There are many additional therapeutic indications where they could be used in

children or could better be used in children. But with the existing generic drugs on the market most companies will not take the risk to develop a new formulation as the development costs will probably not be retrieved from the market. The EU pediatric legislation tried a special incentive, the "pediatric use marketing authorisation (PUMA)" in the hope of attracting more development of special pediatric formulations for off-patent drugs. Unfortunately, this model was developed without input from people experienced in business. The consequence was that the number of successful PUMA projects is extremely limited.

25.6 Ethical Challenges of Clinical Trials with Children

In legal terms, the key difference between a child and an adult is that the child is not yet a legal subject in its own right: it cannot act on its own, but only through the parents [34, 48, 49]. In former times, children per se had no rights at all; today the world is full of well-intended international declarations of the rights of children, and many universities offer own postgraduate study programs on the rights of children.

In the past the prevailing opinion was that it was unethical to abuse children as guinea pigs. Today's view has shifted towards a position that it is equally unethical to expose children to untested drugs.

The legitimacy of clinical research with children is today much less disputed than decades ago. Children cannot give informed consent, as they are not yet full legal subjects in the sense of the law. It is the parents who must give informed consent. The debate about e.g., if one or both parents need to give this consent, to what degree this is practical, and what to do in special cases such as when the mother of the child is a minor herself fill entire libraries [50–52]. It is expected today that children in clinical trials today should be asked to give their assent, and this should be documented in written form [10]. This requires age-appropriate explanation of the potential benefits and risks of the study participation. Usually one more elaborate versions are used for adolescent patients, and a simpler one for children from about 7 to 11 years of age. For an in-depth reading of ethical challenges of pediatric clinical trials we refer to the broad literature [53].

25.7 Operational Challenges of Clinical Trials with Children

With the increasing awareness of the need of clinical trials in children there is now more experienced personnel available than used to be the case decades ago. Key issues of operationally dealing with children in clinical trials derive from the key differences between children and adults.

Children cannot survive alone. They are mostly part of a family, and so a clinical trial must take into consideration the entire family. No mother will adhere to a rigid visit scheme that does not allow flexibility if brother or sister of the patient is ill.

No mother will return to a shabby hospital with unfriendly nurses that chase away the playing brother or sister.

The most visible physiological difference is the size of children. A 10 kg child has less blood than an adult, and a 500 g preterm newborn has even less blood to spare for routine laboratory and hematology investigations. The normal laboratory values in children are often different. The maturity of the organs is different, with different drug–drug interactions for different drugs. Depending on the organ system and the way of administration, there is a myriad of aspects to be taken into consideration. The skin of preterm newborns is much thinner and more permeable than adult skin. Measuring of blood pressure with adult devices is an adventure, at best. We refer to good textbooks of pediatric physiology. Also the issue of blood withdrawal is discussed broadly in the literature [54].

Children's attention span is also different from adults. A child will not listen for an hour to the explanation of a clinical trial. The physician has maybe 5 min. So he has to prioritize his messages.

A child's world differs from the adult world in many more aspects. The emotions are stronger, the understanding of institutions is less systemic, and the understanding of time and geographic dimensions is different.

Both the investigation site and the visiting study monitor should be aware of all these special traits. They should have special training.

25.8 Conclusions

Planning and performing clinical trials with children requires a solid fundament of the basics of GCP in general and additional special knowledge and training. The changed regulatory environment is at present pushing the demand for better age-adapted formulations of children.

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