Pediatric Clinical Trials

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Abstract

Over the past decades, drugs have been used in children at different ages, outside the terms of their marketing authorizations in relation to indication, dosage, age, and route of administration, both in Europe and worldwide. The off-label use of drugs exposes children to unexpected adverse reactions or to suboptimal treatment. To develop safe medicines for children, ensuring that pediatric medicines are of high quality, ethically researched, and authorized appropriately, many legislative efforts have been made at European and international level. This chapter will address specific regulatory and ethical aspects included in legal frameworks and ethical guidelines.

Introduction

The lack of drugs tailored for children is a long-standing problem. For years the lack of studies, specifically designed to investigate pharmacological and toxicological aspects in the pediatric population, has forced children to use many approved drugs without a proper information on dosage, efficacy, and safety and on the basis of data extrapolated from adult studies in a more or less empiric way.

Extrapolation of adult to child data is problematical for several reasons. Pharmacokinetic (PK) and pharmacodynamic (PD) processes, in children, differ considerably from those in adults. In addition, developmental pharmacology has taught that the pediatric population cannot be considered as a homogeneous group. According to ICH-E11 guidelines, different age groups that have their own PK and PD particularities have been defined: *preterm and term neonates* from 0 to 27 days,

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infants from 1 to 23 months, *preschool children* from 2 to 5 years, *school children* from 6 to 11 years, and *adolescents* from 12 up to 18 years. The safety and efficacy of drugs is development dependent. Clinical trials are needed with the aim to investigate optimal dosages and formulations in various pediatric age groups [8].

Research involving children raises unique ethical issues. These result primarily from related ideas of competence, autonomy, and vulnerability. Children have traditionally been considered as more vulnerable than adults because of their lack of competence to take part in decision-making around complex issues, such as health care and inclusion in research. This vulnerability means that others (parents, legal guardians, health-care professionals, and educators) must be trusted to act in the child's best interests and make decisions for them. This vulnerability has often meant that children have simply been excluded from research, out of well-intentioned but shortsighted attempts to protect them. The result of excluding children from research is that society fails to learn about them and fails to develop new, better ways to approach, treat, and protect them [5].

In Europe, the *Directive EC/2001/20 on Good Clinical Practice* (GCP), entered into force in May 2004, was the first attempt to take into consideration the need of performing clinical trials (CTs) in children with current GCP requirements. An article is included (Art. 4) with the aim to guarantee that pediatric clinical research in Europe is conducted at the highest ethical level, using appropriate methodology, avoiding discomfort for children, and after having obtained informed consent from parents and assent from children where applicable. The *Note for Guidance ICH Topic E11*, giving recommendations on trial characteristics, also specifies that children should be given medicines that have been appropriately evaluated for their use, in all pediatric age groups.

Compared to requirements in research with adult participants, research with children faces additional ethical challenges. These challenges are related especially to children's decision-making capacity, their vulnerability, and the particular role of parents or guardians in the research process. The strong demand for protecting children from harm needs to be balanced with the equally urgent need for well-founded research findings that can help improve health care for children.

To facilitate and encourage the conduct of clinical research, considerable legislative efforts have been made, both in the European Union and in the United States, in terms of regulatory framework and ethical requirements aimed at developing pediatric drugs.

Regulatory Framework to Develop Medicines for Children

In recent years, there has been an important shift in opinion, both in the United States (US) and the European Union (EU), about conducting clinical trials involving children [7]. The lack of drug trials in children now is being seen as a major ethical problem, and the USA and the EU have introduced incentives and legislations to both stimulate and force the pharmaceutical industry to develop studies into medicines for children. This legislation was meant to lead to an increase in investigating the pharmacological effect and safety of both new and existing medicines in children.

In the USA, legislation on pediatric drug research has gradually been introduced since 1997.

The *Food and Drug Administration Modernization Act* (FDAMA – 1997) provided financial incentives, by granting an additional period of 6 months of marketing exclusivity, if a pharmaceutical company conducted and submitted pediatric studies of a medication (Pediatric Exclusivity Provision). The *Pediatric Rule of the FDA* was introduced in 1998. It required drugs, for new therapies and indications, to be studied in children. The US *National Institutes of Health* (NIH) issued a policy that required inclusion of children in all human subject research conducted or supported by the NIH, unless there were scientific or ethical reasons to exclude them. Although these first regulations have resulted in some success, in a number of important children's diseases, trials were still not conducted because of insufficient financial incentives. For this reason, in 2002, the *Better Pharmaceuticals for Children Act* (BPCA) introduced, in the USA, a legal obligation for companies to conduct trials with drugs for children where there is a therapeutic need. It provides financial incentives to companies to undertake clinical trials to improve safety and efficacy of products used in the treatment of children while the products are still *patent protected*. The *Act* also provides for research on older off-patent medicines, through a priority list developed by the NIH. The *Pediatric Rule* was succeeded by the *Pediatric Research Equity Act* (PREA, 2003 amended in 2007), which enables the *Food and Drug Administration* (FDA) to request pediatric data in studies on drugs and biologicals.

The 6-month additional marketing exclusivity is provided only if studies in children are completed in accordance with a written Pediatric Study Request issued by the FDA.

Pediatric development plan must be submitted with or before submission of the New Drug Application.

All pediatric development plans are reviewed by the review division for the disease area being studied. All Pediatric Study Requests issued by FDA, as well as deferrals and waivers for pediatric studies, must be approved by an internal but central FDA Pediatric Committee.

To necessitate trials of medicines relevant to the childhood population, the EU legislation provides both a legislative framework and financial incentives for pharmaceutical companies to perform them.

The *Paediatric Regulation* (*1901/2006/EC*) is the latest in a number of incremental regulatory steps to improve public health for children through increasing research, information, and availability of medicines.

The new key element of the *Paediatric Regulation* is the early involvement of a pharmaceutical company in the research and development program of a medicinal product by requiring to consider the needs of the pediatric population, also in terms of age-appropriate formulations, in accordance with a *Paediatric Investigation Plan* (PIP). The PIP is defined as a research and development program aimed at ensuring that the necessary data are generated to determine the conditions in which a medicinal product may be authorized to treat the pediatric population. It describes the pediatric development (quality, nonclinical, and clinical aspects) and all

adopted measures necessary to investigate the medicine in the pediatric population. It has to be agreed with an ad hoc committee of experts, the *Paediatric Committee* (PDCO) established at the *European Medicine Agency* (EMA) [4].

This committee aims at ensuring expertise and competence in pediatric medicines and at providing scientific opinions on any development plan for medicines for use in children. The PDCO must consider whether or not any proposed studies can be expected to be of significant therapeutic benefit and/or to fulfill a therapeutic need of the pediatric population. To this aim, other PDCO-specific tasks include establishing an inventory of specific needs for pediatric medicinal products and giving scientific input in the development of any documents related to achieving the regulation's objectives.

The PDCO membership includes members and alternates of the *Committee on Human Medicinal Products* (CHMP), delegates appointed by the Member States that are not represented in this committees as well as representatives (three members plus alternates) of health professionals and patients' associations nominated by the European Commission, following a public call for expressions of interest and after consulting the European Parliament.

The final composition of the committee, including members and alternates, is expected to cover those scientific areas relevant to pediatric medicines. Members, alternates, and experts must not have any financial or other interests in the pharmaceutical industry that could affect their impartiality.

When an agreed PIP is completed and all the information has been submitted to the regulatory authorities, the medicinal product – falling under Article 7 or 8 of the regulation – will be granted an extra 6-month patent protection (extension of the duration of its *Supplementary Protection Certificate* [SPC]). For orphan medicinal products, the incentive takes the form of extra 2 years market exclusivity.

The regulation also establishes a new type of marketing authorization called the *Paediatric Use Marketing Authorisation* (PUMA), intended to stimulate the development of off-patent products for use in the pediatric population. The PUMA will allow companies to benefit from 10 years of data protection, as a reward for the development of a new indication in children or formulations appropriate for children of all ages.

The Paediatric Regulation includes provisions for funding of research into off-patent medicines (Community Framework Programmes for Research, Technological Development and Demonstration Activities, or any other community initiatives for the funding of research). It established a system of optional free-scientific advice from the EMA for studies in pediatric patients. The regulation also created a public database for listing of pediatric studies.

According to EU legislation, guidance has been published concerning to ethical aspects of clinical trials from birth up to adulthood [6]. This guidance was developed by the ad hoc group, chaired by the European Commission, responsible for implementing guidelines relating to Good Clinical Practice. All the major ethical issues, taking into account the vulnerability of children, are addressed according to the main ethical principle of beneficence (non-maleficence), respect of persons, and justice.

Since scientific advice for pediatric development is free of charge both in the USA and Europe, the possibility of discussing the product development strategy, at an early stage, directly with the relevant authorities, can help to clarify requirements before starting any clinical program and to develop well-designed pediatric trials.

Ethical Issues of Pediatric Research

The primary goal of existing research ethics structures and practices is to ensure that participants, adults or children, will not be exposed to undue risks and, where possible, will receive some benefit from their research participation. In research with children, the protections are significantly stricter than in research with adults due to their perceived vulnerability, and most international guidelines agree that children require particular protection in research and accordingly set fairly strict criteria regarding the issues of benefit and risk.

According to the principle that the interests of science and society never prevail over the interests of individual research subjects, there exists a considerable consensus that pediatric research should only be undertaken in so far that the research serves the interests of minors, either by generating a direct benefit for the child concerned or by yielding an indirect benefit to a larger group of beneficiaries, such as the population of minors or the group of patients to which the minor belongs.

Direct benefit enjoys a prominent position in the assessment of research protocols by ethics committees. The standard is used to weigh the acceptability of risks, based on the rationale that the greater the potential benefit involved, the lower risk threshold should be. Major legal regulation requires that, basically, non-beneficial research does not exceed stringent minimal-risk and minimal-burden threshold. Risk thresholds often play a prominent role in the assessment of the ethical acceptability of pediatric clinical trials. The acceptability of the risks and burdens, inherent to research participation, is often a complex and difficult issue, particularly when research is conducted in a vulnerable population, such as minors.

It is the principle of proportionality that is used to determine whether the risks inherent to a clinical trial are considered acceptable. To this aim, it is important to consider not only the risk of harm, as a consequence of research interventions, but also the burden of research participation itself. The clinical trial must be designed to minimize pain, discomfort, fear, and any other foreseeable risk in relation to the disease and developmental stage. The risk threshold and degree of distress must be specially defined and constantly monitored.

Another important ethical issue is related to the respect of the autonomy of the children involved in such clinical trials. Since the research scandals during the Second World War, the principle of the respect for persons has been adopted and made operational in the ethical and legal doctrine of informed consent.

Due to the incompetence of minors to provide legally valid informed consent, the involvement of a competent adult, acting as a surrogate decision-maker, is most often required to enroll a minor in a clinical trial. Such involvement of a proxy does

not preclude the minor playing an active role in decisions about clinical trial participation. Several decision-making strategies (including dual consent, consent by the proxy, and assent by the child and respect for the dissent of the child), have been introduced in order to encourage shared decision-making and a fair differentiation of decision authority, between the proxy decision-maker and the child taking part in the trial. Proxy consent is provided by the parents or another legal representative, preferably in writing. Informed consent requires that parents or other responsible adults be informed of all the features of the research that may affect willingness to allow the child to participate. Not only the right of the responsible adults to refuse consent should be respected, but also they should be informed that their consent may be revoked at any time without negative consequences to the minor concerned and must represent the presumed will of the minor.

The child concerned must receive information regarding the trial, the risks, and the benefits appropriate to his/her capacity of understanding and provided by staff with experience with minors. The explicit dissent to start or continue research participation, expressed by a minor who is capable of forming an opinion and assessing the information relevant to participation in the clinical trial, must be considered by the (principal) investigator at any time.

Many differences exist across Europe regarding the informed consent procedure. Several EU Member States specifically define age criteria, or an age cutoff, with regard to the decision-making capacities of minor research subjects [2, 3].

Some European countries provide more restrictive rules aiming at protecting minors involved in clinical research. They assure more importance to the will of the minors (Spain) or consider their will necessary to involve them in clinical trials (Denmark, Estonia, and the Netherlands). The expression of will is accepted at different age limits (12 years in Spain, 15–17 years in Denmark, 7–17 years in Estonia, 12 years in the Netherlands). In France it is provided that the will of the minors prevails and it is impossible to pass over their refusal, or the withdrawal of their consent, while in Germany it is specified that "*the minor should declare or express in any other way that he does not wish to take part in the clinical trial, this must be respected*." Besides, "*if the minor is in a position to comprehend the nature, significance and implications of the clinical trial and to form a rational intention in the light of these facts, then his consent shall also be required*." Finnish legislation states that, taking into account the minor's age and maturity, his/her opinion opposing a research or a research measure shall be complied with. It specifies that the written consent of a minor, having reached the age of 15 and capable of understanding the importance of the research procedure, shall be sufficient for him/her to be involved in a clinical trial if this research is likely to be of direct benefit to his/her health.

According to the principle of autonomy, before seeking consent or assent from the child, the investigator should inform the child of all features of the research that may affect his or her willingness to participate and should answer the child's questions in terms appropriate to the child's comprehension. The investigator should respect the child's freedom to choose to participate in the research, or not, by giving the child the opportunity to give assent to participation, as well as to

choose to discontinue participation at any time without prejudice. Assent means that the child shows some form of agreement to participate and, most of all, that he/she does not object. Investigators working with infants should take special effort to explain the research procedures to the parents (legal representatives) and be especially sensitive to any indicators of discomfort in the child. In spite of the paramount importance of obtaining consent, instances can arise in which consent or any kind of contact with the participant would make the research impossible to carry out. Nonintrusive field research is a common example. Conceivably, such research can be carried out ethically if it is conducted in public places, participants' anonymity is totally protected, and there are no foreseeable negative consequences to the participant. Judgments, on whether such research is ethical in particular circumstances, should be made in consultation with an ethics committee (Institutional Review Board).

Before research in children can start, the research protocol must be reviewed and endorsed by the competent authority and at least one ethics committee. To guarantee an adequate assessment of issues that are specifically related to the conduct of clinical research in minors, ethics committees require pediatric expertise, within the ethics committee, or by consulting taking external advice about the clinical, ethical, and psychological problems in the field of pediatrics.

With reference to pediatric expertise, in Europe only four countries have ethics committees specifically devoted to minors (Finland, Slovakia, the Netherlands, and Italy). In the other countries, pediatric expertise is guaranteed mainly by inclusion of pediatric experts in ethics committees or by an advice from external experts, requested case by case, especially when there is no pediatrician in the committee. In France this expertise is required only for minors under 16 years, while in Denmark, pediatric expertise evaluation is not required in the case of nonintervention trials [3].

Regarding the need to guarantee the confidentiality of personal data, it is established that where personal information on a child is collected, stored, accessed, used, or disposed of, a researcher should ensure that the privacy, confidentiality, and cultural sensitivities of the subject and the community are respected. Children participating in a trial are entitled to know any information collected on their health. Other personal information, collected for a research project, will need to be made accessible to them in conformity with national laws on the protection of individual data.

With reference to the insurance to be subscribed before starting a clinical trial, the *European ethical recommendations*, approved in 2008, underline that insurance companies' contracts should not waive liabilities regarding long-term effects, or limit the liability period, and ethics committees should pay careful attention to the insurance contract regarding this issue, in particular with respect to long-term effects on development.

It is important to underline that all international and European ethical guidelines agree that no incentives or financial inducements may be provided except for compensation to take part in the research. It is stated that it is considered unethical to replicate unnecessarily trials in children. This can only be avoided by ensuring that information gained in any trial, whether positive or negative, is made available to both researchers and the public.

Conclusion

The analysis of the ethical and legal frameworks, related to pediatric research, shows that a number of contradictory provisions exist at supranational level and a considerable diversity of legal requirements must be complied with at the national level, dependent on where the research takes place. The harmonization process should not be limited to harmonization of relevant legal provisions but also cover the operational implementation of legal requirements. Particularly the work of ethics committees is open to further streamlining in this respect [1]. The approval of a research protocol is not a full guarantee for clinical research to be ethically sound. Many of the ample, complex, and diverse tasks, in the implementation of the ethical and legal frameworks governing research in children, are left to the clinicians who conduct clinical trials. They are granted considerable latitude in interpreting and implementing the ethical and legal frameworks. This large discretion of clinicians is respectful of the established routine of making medical decisions on a case by case. It raises significant drawbacks. A lack of communication skills, poor knowledge of the relevant ethical and regulatory requirements, conflicts of interest, and time constraints all can be serious hurdles to a successful implementation of GCP standards [9].

The ethical conduct of clinical research is a shared commitment of all those involved. All parties involved have a responsibility in assessing the acceptability and appropriateness of the research. Education and training should be important tools to guarantee the quality and safety of clinical research as well as the well-being of children involved.

Ready Reckoner

- Specific regulatory frameworks have been adopted to increase the number of clinical trials in children.
- Additional market exclusivity has been introduced in the USA and in EU.
- To obtain financial incentives, pharmaceutical companies have to submit a pediatric development plan to the regulatory authorities.
- This pediatric plan should be approved by an ad hoc committee established in EMA and/or FDA.
- Specific ethical requirements have been established to guarantee the quality and safety of pediatric studies.
- Major ethical requirements are related to:
  - The benefit/risk balance (that should be favorable)
  - The necessity of a direct benefit for the child involved or the group of children with the same illness/condition
  - The necessity to minimize risk and burdens as well as pain, distress, and discomfort
  - The authorization of the parents (legal representatives) that should be obtained by writing

  - The exhaustive information to be provided to the parents (legal representatives) concerning, e.g., the nature and scope of the research, the right to refuse/withdraw without incurring in any prejudice and the measures adopted to guarantee the confidentiality
  - The assent of child involved that should be obtained according to their age and degree of maturity
  - The age-appropriate information that should be provided to the children called to take part in the research
  - The interdiction of providing child or legal representatives with incentives to participate in research
- It is unethical to replicate, unnecessarily, trials in children.

Cross-References

► Ethical Standards for Clinical Trials
► Off-Label Use of Medication

References

1. Altavilla A, Manfredi C, Baiardi P, Dehlinger-Kremer M, Galletti P, Chaplin J, Ceci A. Impact of the new european paediatric regulatory framework on ethics committees: overview and perspectives. Acta Paediatr. 2012;101(1):27–32.
2. Altavilla A, Giaquinto C, Ceci A. Activity of Ethics Committees in Europe on issues related to clinical trials in paediatrics: results of a survey. Pharm Policy Law. 2009; 11: 1–9
3. Altavilla A, Giaquinto C, Ceci A. European survey on ethical and legal framework of clinical trials in paediatrics: results and perspective. J Int Bioethique. 2008;19(3):17–48.
4. Baiardi P, Giaquinto C, Girotto S, Manfredi C, Ceci A. Eur J Clin Pharmacol. 2011; 67 (11 suppl): 1–133. Especially: Altavilla A. Ethical key issues and fundamental rights in paediatric research. pp 1–7
5. Coleman CH. Vulnerability as a regulatory category in human subject research. J Law Med Ethics. 2009;31(1):12–8. Spring.
6. European Commission. Ethical considerations for clinical trials on medicinal products with the paediatric population. Eudralex, vol 10. 2008
7. Friedman Ross L. Children in medical research. New York: Oxford University Press; 2006. 285 p.
8. ICH (E11), Clinical investigation of medicinal products in the paediatric population, CPMP/ICH/2711/99
9. Pinxten W, Nys H, Dierickx K. Frontline ethical issues in pediatric clinical research: ethical and regulatory aspects of seven current bottlenecks in pediatric clinical research. Eur J Pediatr. 2010;169(12):1541–8.

Further Reading

Knellwolf AL, Bauzon S, Alberighi OD, Lutsar I, Bácsy E, Alfarez D, Panei P. Framework conditions facilitating paediatric clinical research. Ital J Pediatr. 2011;37:12.