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SPECIAL ARTICLE

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Ethical principles and operational guidelines for good clinical practice in paediatric research. Recommendations of the Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP)

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Abstract A child has the full right of protection of his/her life by provision of optional medical care. There is a need in paediatrics for better evidence based practice founded on quality research into efficacy and safety of children's medications. To protect the best interests of the child one must balance the ethical demand to do clinical studies with the necessity to avoid doing harm. To achieve this end good clinical practice in paediatric research demands that studies comply with the Declaration of Helsinki, ICH topic E11, EU Directives and other relevant international guidelines. Evident differences in physiology, pharmacology, pharmacokinetics and pharmacodynamics between children of differing ages and between children and adults demand properly constructed and conducted studies that respect the special somatic, emotional and mental needs of children. To justify any research project one must balance the benefit/risk ratio, provide experienced, competent personnel and infracture, obtain adequate informed consent/assent, and have the study evaluated and approved by an ethics committee containing expertise on the rights and needs of children.

Keywords Children · Ethics · Good clinical practice · Research

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Principles

Ethical Issues

The reader is referred to document of P. J. Sauer on the principles concerning biomedical research involving children.

The Rights of Children

According to the Rights of Children proclaimed in 1959 by UNICEF and approved in 1989 by the 41st assembly of the UN, all human rights and full identity are granted to the child. For that purpose doctors need enhanced empathy and readiness to apply additional safety measures.

The necessity for research in children

Optimal medical care is based on the scientific evaluation of preventive, diagnostic and therapeutic measures. However, with respect to the paediatric population, there are significant deficits in the objective knowledge of quality and efficacy of current preventive measures, pharmacokinetics and pharmacodynamics of medications, appropriate dosage and application form for different age periods, and of the adequacy of deriving children's doses from adult studies. The majority of the relevant data on the safety of interventions and medicinal products prescribed for children is derived from studies in adults. The medications used in children's hospitals are not officially licensed for children in 50% of cases on the average, and in neonatal units in up to 90%. Adverse drug reactions are commoner to unlicensed and off-label drugs on paediatric wards. Moreover, the general extrapolation of known data from adults to children is acceptable only with certain restrictions, because of evidence differences in physiology, pathology, pharmacokinetics and

pharmacodynamics and because some diseases exist only in children.

Regarding the usage of medicinal products age specific differences have to be considered:

1. Pharmacokinetic differences:

In preterm and term infants, at birth and during the first weeks of life the protein binding and the excretion of metabolites are reduced due to the immaturity of metabolic pathways, renal function and to the variable absorption of medications. In older infants and early childhood the acceleration of the metabolic rate may require higher dosages per unit body weight or body surface area than in adults to reach similar plasma concentrations and clinical effects. Moreover, increased metabolic rates may require more frequent administration.

2. Altered pharmacodynamic reactions:

In early developmental stages some receptor functions, effector systems and homeostatic mechanisms, even if efficient for this age, are not efficiently developed to reach the desired pharmacologically caused changes of the function of organs or tissues.

3. The process of growth and development:

Normal growth and development, both physical and mental, may be adversely influenced by medicinal products. The consequences depend on the time and the duration of the applications and are not always reversible.

4. Specific pathology:

Children may need medicinal products for their illnesses that are different from those for adults because of increased frequency, greater severity, different natural courses or specific pathology. Therefore, different methods of administration and formulations (suspensions, chewable tablets, fizzy drinks, suppositories, patches etc) need to be developed.

The best interest and the protection of the child

Children involved in research are of special concern because of their age specific peculiarities, the protection of their developmental potentials, the respect of their increased vulnerabilty and fears, and the biological differences between children and adults as mentioned above, that can be summarised as "best possible protection and promotion of the best interests of the individual child".

Conclusion

Two important apparently contradictory ethical demands require balance; on the one hand needs to obtain evidence based information on the efficacy and safety of medicinal products for children, and on the other hand intrinsic respect and protection of the child involved in research.

Guidelines

The latest version of the Declaration of Helsinki from the World Medical Association, the guidelines for Good Clinical Practice of the International Conference on Harmonisation (ICH) and the EU directives on the implementation of Good Clinical Practice are basically relevant for children, mainly concerning the responsibilities of the persons, institutions and authorities involved in biomedical research. Moreover to respect the best interests of the child involved in research and to further his/her special needs, the following additional child specific guidelines are suggested.

The aim of clinical studies

Biomedical studies involving children as research participants should be focussed only on the knowledge of the epidemiology, pathogenesis, prevention, diagnosis, cure of alleviation of child relevant diseases or conditions. Children should not be used as research objects on behalf of adults. Children should not be involved in research that serves only scientific interests and does not provide any benefit to them.

The integrity of the child

The protection of the integrity of the child must be considered in all life stages including those children who are disabled or cannot participate actively in the Informed Consent/Assent process for other reasons. Children need special protective measures because of their increased vulnerability (see below).

Forms of research in children

Observational research

The objective is to seek epidemiological data under different conditions and to study concentrations of body-specific or foreign substances under physiological and pathological conditions at various ages.

Interventional research

1. Pharmacokinetic/pharmacodynamic studies
2. Controlled clinical studies
3. Uncontrolled clinical studies

Only children with rare diseases should be subject of such studies (e.g. cystinosis, metabolic disorders).

4. Post-marketing surveillance

These studies can provide valuable information about safety and efficacy (also for subgroups), and explore long-term effects.

Efficacy, pharmacokinetic and safety studies (toxicity, teratogenicity, cardinogenicity studies)

In general these studies should be carried out in animals first – or by means of comparable alternative methods – and afterwards in adults, if the disease does not exclusively concern the child.

Timing of the involvement of children into interventional studies

The following categorisation is proposed:

1. For diseases exclusively affecting children, trials of medicinal products may start before any adult human exposure, beginning with phase 1, following the demonstration of pre-clinical safety data.
2. For diseases mainly affecting children or diseases that are of particular gravity in children or that have a different natural history in comparison with adults, clinical trials are needed at an early stage (phase 1 or 2) in clinical development following the demonstration of pre-clinical safety data and evidence of efficacy in adults.
3. For diseases occurring in adults and children for which there is currently no or only limited treatment the same is true for (2).
4. For diseases occurring in adults and children for which sufficient treatment exists, clinical trials in children should usually follow the completion of adult phase 3 trials.

Heterogenicity of the paediatric population

With respect to the differing physiological and pathophysiological aspects in different development stages of children, studies need to be considered for specific homogenous sub groups.

1. Very low birth weight (< 28 weeks) or 750 g
2. Premature newborns (< 36 weeks)
3. Term newborns (first 27 days)
4. Infants and toddlers (28 days–23 months)
5. Small pre-school children (2–5 years)
6. Primary school children (6–11 years)
7. Adolescents (12–16/18 years)

These ages are arbitrary but important. The preterm has different body composition, immature hepatic and renal function, with variable drug absorption, distribution and excretion. The adolescent has problems with consent, compliance, contraceptives.

Benefit versus risk in research

All members of research teams have a major responsibility to protect child participants from harm beyond a defined acceptable risk. The crucial preconditions to ensure benefit and to prevent inappropriate risk include: (1) the study must be aimed at reducing suffering and improving management, (2) the predicted benefits must be greater than recognizable risk, (3) risk must be minimised by all available means and (4) minimal risks usually means data collection from observational studies. Venepuncture is usually considered minimal risk. Greater than minimal risk implies invasive procedures or potentially toxic therapies.

Planning and conducting studies

Only those studies that are properly planned and conducted by competent researchers are ethically justified. They should be conducted basically according to the principles of GCP guidelines as recommended by international organisation (WMA, CIOMS, NIH, ICH, EFGCP). Moreover, study protocols and study designs should be evaluated child-specifically and should not be simple modifications of study protocols for adults.

The adequate performance of a study must be guaranteed by competent medical experts who are familiar with the GCP guidelines, work in the "best interest of the child" and are capable of empathic and trustworthy communication with children and parents. The study must be carried out in an institution or primary care practice that provides a child-specific atmosphere accepted by children and parents, experienced personnel and an infrastructure that allows the adequate carrying out of the study by preventing risks and somatic and psychological burden as far as possible.

Minimising risks

For this purpose the following aspects should be taken into consideration:

1. Adequate pre-clinical toxicity studies should be known before beginning a paediatric clinical trial.
2. Safety data from adult studies should be available before beginning a paediatric clinical trial unless the disease or condition occurs in childhood solely.
3. The number of subjects should be as few as possible, but large enough for an adequate statistical evaluation.
4. Children should not be exposed to dosages of medications they do not need in the judgement of the doctor in charge.
5. The number and extent of examinations, especially of invasive interventions, should be limited to the minimum necessary for the study.

6. Adequate methods for laboratory tests using small blood sample volumes (e.g. micromethods) should be used and population kinetic methods should be adapted to reduce the number of blood samples per subject.
7. Child-specific protocols should be drawn up by experienced experts and the study should be carried out under the supervision of paediatricians.
8. The study protocols should be evaluated by ethics committees whose members are experienced in paediatric research and concerned with the special needs of children (see below).

Minimising discomfort

Every effort must be made by research institutions and staff to minimise pain, discomfort and fear among children with preparation, play facilities and skilled staff.

Informed consent/assent of parents and child-patients

Rules and regulations concerning the obligation to obtain informed consent/assent from children, their parents or guardian, are included in the laws of most European countries with national variations. According to the literature, the ability to understand the aim, possible benefit and risk of a research study can be expected at the earliest from the age of 9 years onward.

The Ethics Working Group of the CESP has published "Guidelines for Informed Consent in Biomedical research Involving Paediatric Populations as Research Participants" to which readers are referred.

There must be no pressure to participate, or inproper influence (such as monetary reward). Verbal and written consent is essential, children should give assent so far as their age, understanding, intellectual abilities allow, the consent of one or both parents is dependent on national laws, refusal to participate or withdrawal from the study should not impair medical management, and consideration and protection of vulnerable children is essential.

The content of information sheets/processes should contain separate information sheets for parents/guardians and children, the responsible investigator should be the primary informant, and complete information on the nature of the study, aims, potential risks, outcome measures, insurance arrangements, management of complications, contact details of investigations, and signatures of all parties be available.

The role of ethics committees in evaluating biomedical research projects in children

The CESP recommended in 1998 in Helsinki that all national paediatric societies should establish ethics committees and the interests of children should always be represented in institutional review boards/independent ethics committees. This means that paediatric experts and persons who are well acquainted with the needs of children involved in research should be represented on ethics committees that evaluate paediatric research.

Ethics committees should basically evaluate the following:

1. The competence of the responsible study investigator and his/her team and the infrastructure of the institution or primary care practice that must be experienced in paediatric research in general and in special in the field of the applied project.
2. Compliance with legal regulations
3. The pre-clinical safety and efficacy data that are preconditions for a paediatric clinical trial (investigator's brochure)
4. The clinical results of adult studies as far as required (literature, investigator's brochure)
5. Type and phase of the study
6. Justification of the study
7. Benefit-risk relationship
8. Study design and biometric planning
9. Inclusion and exclusion criteria
10. Criteria for the termination of the study
11. Adequate methods and safety measures
12. Study-relevant risks and discomforts
13. Statistical methods
14. Comprehensive, understandable age specific Informed Consent sheets for legal representatives and child-participants
15. Anonymity of the data
16. Sufficient insurance of child-participants valid in the relevant country
17. Case report forms
18. Attention of all child specific concerns
19. Consideration of opinions and certificates of other ethics committees for multicenter studies.

Conclusion

These guidelines adapted for children are based on principle recommendations for Good Clinical Practice included in the Declaration of Helsinki, the WHO Good Clinical Practice Guidelines, the CIOMS International Guidelines for Biomedical research Involving Human Subjects, the UN Convention on the Rights of Children, the Convention on Human Rights and Biomedicine of the Council of Europe, the CPMP/EWP Note for Guidance on Clinical Investigation of Medicinal Products in Children, the Recommendations of CESP concerning Research in Children, the WHO Operational Guidelines for Ethics Committees that Review Biomedical research, the EFGCP Guidelines, the Recommendations of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Topic

E11, Clinical Investigations of Medicinal Products in the Paediatric Population and the EU Directive 2001/20/EC of the European parliament and the Council on the Implementation of Good Clinical Practice in Conduct of Clinical Trials on Medicinal Products for Human Use.

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