

CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN CHILDREN

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CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN CHILDREN

This note for guidance should be read in conjunction with Part 4 of Directive 75/318/EEC as amended, which requires "... details concerning patients who may be at increased risk" and is intended to assist applicants in its application in respect to specific problems presented by medicinal product testing in children.

1 THE NEED FOR MEDICINAL PRODUCT TESTING IN CHILDREN

Medicinal product testing in children is a difficult topic. A controlled trial in children involves certain technical and ethical problems which are not of such magnitude in adults.

However advantageous a clinical trial may be to prove or disprove the value of the treatment, it is clear that members of one or both of the groups - control or active investigational product could suffer injury as a result of inclusion in the trial, even if the whole community benefits. Adults who participate in clinical trials and who understand the issues involved giving their informed consent, accept and share the risk of injury, although in practice serious damage to trial subjects is rare. Children are largely dependent on their guardians who take the legal responsibility for their welfare and safety. As children are not legally competent to assent to a clinical trial, informed consent should be obtained from the legal guardian in accordance with national legislation.

It is essential at all times to retain the confidence of the guardian and child. "Where physical or mental incapacity makes it impossible to obtain informed consent or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation." (Declaration of Helsinki – 1975 revision – Recommendations Guiding Medical Doctors In Bio-Medical Research Involving Human Subjects).

There is therefore a natural and proper reluctance to submit children to clinical studies as they cannot give fully informed consent themselves or realise the significance of risk v. benefit. Apart from these ethical considerations, a trial may involve repeated invasive procedures which may be painful or frightening to a child.

Yet it is important to carry out tests in children for the following reasons.

1.1 Scientific Reasons

From a physiological and pathological standpoint, children, and especially very young children, cannot be considered as small adults because of:

a) pharmacokinetic differences:

these are well known in the premature infant and in the first weeks of life (e.g. modification of absorption, limited capacity of elimination due to the immaturity of metabolic pathways and renal function, and small volumes of distribution). In later infancy and early childhood, faster rates of biotransformation and relatively

increased volumes of distribution may necessitate the administration of higher doses per unit of body weight or surface area than in adults, in order to obtain identical plasma levels;

b) altered pharmacodynamic responses:

the receptor functions and effector systems are immature, and homeostasis mechanisms may not be sufficiently developed to “smooth” the pharmacologically induced change of organ or tissue function;

c) specific age-related vulnerability:

as organ functions mature, there is a risk that medicinal products may adversely affect development (e.g. weight gain and retarded growth with corticosteroids; impaired psychomotor development with amphetamine substances in hyperkinetic children);

d) specific pathology:

children may need medicinal products for diseases which differ from adults either because of increased frequency (e.g. otitis media and malnutrition), increased severity (e.g. diarrhoea), specific pathology (e.g. inborn errors of metabolism, growth hormone deficiency, neonatal apnoea and patent ductus arteriosus). Enzymatic anomalies are often first revealed in childhood.

For all these reasons it is widely accepted that the effects of many medicinal products upon children may differ considerably from those observed in adults, even when dosage has been adapted to body weight or body surface area. So the adult experience of the medicinal product may not accurately predict the minimal effective dose, maximum titrated dose, therapeutic effect or adverse reactions in the child.

1.2 Ethics

Despite the problems of clinical trials in children it is considered that there are a number of circumstances where there is an ethical responsibility on a manufacturer to perform such studies in order that the balance of risk v. benefit may be clearly understood in regard to paediatric use. It is recommended that studies are performed in the following circumstances:

a) the potential use:

if a medicinal product appears to offer a unique or advantageous treatment for a disease of childhood and is likely to be used in paediatric practice, it may be important to perform tests in children rather than to contra-indicate the medicinal product for paediatric use. This is all the more important because the severity and natural history of children’s diseases makes a “trial and error” approach to therapeutics potentially hazardous;

b) health protection:

children are often involved in vaccination programmes and need the assurance of adequate safety and efficacy of the preparation. While it is anticipated that vaccines should benefit individuals, they also affect the frequency and severity of a microbiological disease in the population as a whole;

c) personal benefit:

except under very specific conditions, the child should stand to obtain some direct benefit from the clinical trial. This principle should reduce the use of “normal childhood volunteers” except in the testing of vaccines where both the child subject and the population stand to benefit;

d) safety for children:

while it is clearly improper knowingly to expose children to medicinal product doses they don't need, doctors and industry should be prepared with an emergency protocol to start, immediately, certain studies (e.g. pharmacokinetic determinations) in the unusual circumstances of accidental overdose or intoxication, or when unusual administration or dose of a medicinal product is required by a child even though such use and dosage schedule has not been fully evaluated. Pharmaceutical companies are encouraged to provide facilities for such emergency assay of the medicinal product and clinicians should report immediately to the authorities and/or suitable journals.

1.3 The need to minimise risks

Considering the vulnerability of children every effort must be made to reduce known hazards and investigators should be fully aware before the start of a clinical trial of all relevant pre-clinical and clinical toxicity which has previously been seen in the development of the medicinal products.

- a) Safety studies should be first conducted in animals as a part of the routine pre-clinical development, then in adults and subsequently in younger patients. The possibility of polymorphic metabolism of the medicinal product should be considered. This sequential approach should identify most toxicity problems but children of certain ages may have toxic reactions that are not seen in adults (e.g. kernicterus, grey syndrome of the newborn);
- b) studies should be efficiently designed using the minimum numbers (to provide statistical significance especially in pivotal studies). A poorly designed trial may provide uninterpretable results and require studies to be done thus exposing more children;
- c) protocols and investigations should be adapted for children and approved by a responsible scientific and ethical committee who would ensure that such investigation is conducted to minimise pain, discomfort, fright, and to control the number and extent of examinations, and invasive procedures;
- d) provision should be made for the management of overdose and severe acute reactions with an emergency protocol available so that additional pharmacokinetic data may be gained;
- e) the usual procedure to stop the study at the earliest possible moment if a hazard arises, should be explained to all staff. In a blind controlled study, there must be no delay in breaking the code;
- f) parents and guardians must provide fully informed consent for the study but the child should also be consulted and informed within the limit of his understanding and maturity in accordance with current national and/or international codes or laws. The child's wish should be respected for certain procedures (related to the research) to be

discontinued from the study. Financial reward to parents or children for participating in trials is not appropriate and may lead to abuse.

2. CLASSIFICATION OF CHILDREN BY AGE AND MATURITY

Children respond to medicinal products differently depending on their age, related to physiological and anatomical development stages. The following age groups are a useful guide bearing in mind that individual development will vary around the norm. They represent the development of an “average” child but there are also sex differences and there is a need to correlate the data relating to the therapeutic dose and adverse reactions with weight and surface area as well as with medicinal product plasma levels.

A medicinal product should not be assumed to be safe and effective for a particular child unless it has been tested at the recommended dose in that development group.

2.1 Neonate (birth to one month)

- a) this is a period of renal, hepatic, enzymatic, and homeostatic immaturity; there is extreme sensitivity to depression of cardio-vascular, respiratory and regulatory mechanisms;
- b) there is also:
 - enhanced medicinal product penetration to the brain,
 - the possibility of rapid transdermal medicinal product absorption,
 - a very high body surface area to weight ratio,
 - a rapid variation with age of protein binding of medicinal products and changes in bilirubin kinetics,
 - difficulty in identifying the nature and mechanisms of toxicity;
- c) immature and other low birth weight infants should be differentiated from normal term newborns and the gestational age should be used.

2.2 Infants and toddlers (1 month to 2 years)

This is a period of CNS maturation associated with the completion of myelination. At this time immune systems develop and muscular skeletal growth and brain growth is rapid.

2.3 Children (2 years to adolescence e.g. 12 years)

This is a period of skeletal growth associated with increasing physical performance and intellectual and physcho-social development. In this age group, school performance is useful in determining medicinal product effects.

2.4 Adolescents (12 years to 16-18 years)

This is a period of sexual maturation when medicinal products may interfere with the actions of hormones and impede development. The group is not homogeneous as the same

age displays wide variations in height and weight. For legal purposes the upper age for regulatory purposes will depend on the age of personal consent.

3. Objectives of Clinical Testing in Children

There are three principal categories of medicinal products in which paediatric testing is necessary.

In sections 3.1 and 3.2, note should be taken of guidelines which already exist for certain therapeutic classes and/or for medicinal products intended for long-term use in adults. These can be adapted for paediatric use where appropriate taking into account the features of the disease in childhood.

In the case of section 3.3, clinical trial methodology should be specifically adapted to the disease and to the therapeutic class.

The clinical trials should also demonstrate that the dosage form is appropriate for administration to the child.

3.1 Medicinal products intended to treat a disease in all age groups

These medicinal products will already have a background of exposure in adults. The purpose of paediatric trials is to determine a safe and effective dosage schedule in the different development groups and to detect unforeseen and unique effects in childhood.

3.2 Medicinal products intended to treat diseases which mainly affect children and/or are of particular gravity in children

In these circumstances it is necessary to initiate clinical trials in children at an early stage to confirm the efficacy of the preparation and to determine the conditions of use.

3.3 Medicinal products for disease affecting children exclusively

These trials are essential to demonstrate efficacy and show the safety profile of the products.

4. NATURE OF CLINICAL TRIALS IN CHILDREN

4.1 Pharmacokinetic studies

4.1.1 Objectives

Especially for those medicinal products whose serum levels can be readily related to the pharmacological or therapeutic effects, medicinal product blood levels will become the basis of subsequent determination of the dosage schedule. Initial titrating doses may well be estimated on the basis of body weight/surface area from an extrapolation of adult data.

All studies should lead to an accumulation of data which account for the absorption, distribution, metabolism and excretion of the medicinal product.

Identification and quantification of the principal metabolites of the medicinal product permit comparison with the elimination pattern of adults. If major differences exist, such studies

serve as a warning of possible adverse effects, and should lead to attempts to identify the unique or unusual pathway of metabolism in the immature patient.

Plasma protein binding should be studied at least in newborns and infants.

Studies with varying degrees of depth and completeness appropriate to the medicinal product and the intended use are essential for each group. Not all medicinal products should be subject to full investigations but judgement should be exercised about requirements for data which are clinically relevant.

4.1.2 Methods appropriate for paediatric trials

The development of appropriate methods on small blood volumes (e.g. some R.I.A., H.P.L, Mass Spectrometry, which utilise as little as 20-100 microlitre) is particularly important. Urinary determinations are also useful (e.g. for assessment of biological half-life and exploration of metabolism). However, collections are not easy (incomplete emptying of the bladder and loss of urine). Determinations of medicinal substance in saliva have been used but do not always provide accurate information and require the co-operation of the patient for collection: nevertheless this can be a useful non-invasive method of sample collection provided there is a good relationship between salivary and plasma/blood concentration.

4.2 Clinical Studies

These are to demonstrate or to confirm that the medicinal product is effective and that the proposed dosage schedule is appropriate being both efficacious and safe.

Clinical trial methodology in children is not fundamentally different from that in adults – in design, statistical analysis or trial management. Protocols should be adapted to:

- a) the therapeutic class and to the clinical situation;
- b) the stage of maturity;
- c) to the proposed objectives of treatment (e.g. relief of symptoms, improvement of the quality of life, prevention of death).

4.2.1 Design

- a) non-controlled studies:

in the case of rare or life-threatening diseases, controlled studies may be impossible or impractical. However after initial exposure of an age group to the medicinal product on a trial and error basis, a suitable dosage schedule needs confirmation using objective criteria. Such studies will rely on historical comparisons initially.

- b) controlled studies:

comparable efficacy to an established therapy need demonstration by a controlled trial.

Absolute efficacy needs a placebo control and this is justifiable if a suitable reference medicinal product is not available or if the efficacy of existing therapies is in doubt.

On the other hand, the use of a placebo should be restricted to the early studies in phase II, in order not to deprive a child of a therapy which is recognised as effective.

The use of a placebo may be acceptable provided it does not cause undue pain or distress or deprive the child of essential effective treatment.

4.2.2 Selection

As far as possible the groups should be homogeneous with respect to:

- the state of maturity,
- weight/height/surface area,
- other factors (e.g. nutritional status, concurrent therapy).

When the disease being treated is rare or life threatening the number of patients can be small.

4.2.3 Criteria for efficacy

Current clinical and non-clinical data should be considered with reference to accepted norms for the age groups (e.g. profile of blood pressure levels in children).

Other criteria may also be useful such as participation in activities, school performance, growth and weight gain provided their assessment is standardised during long-term treatments, and the need for additional therapy.

4.2.4 Safety

Pre-marketing studies should include reports of those adverse reactions manifested at the time of the study. The type of reporting adverse effects, whether by means of spontaneous or elicited reports, questionnaires or other means, must be clearly stated and appropriate for the age groups under study.

Depending upon the nature of the medicinal product and its indications, long-term studies may also be required to determine possible product related effects on skeletal, behavioural, cognitive, sexual and immune maturation and development. Post marketing studies will confirm the safety profile of the medicinal product in use.

5. SCIENTIFIC DATA REQUIRED BEFORE MEDICINAL PRODUCT TESTING IN CHILDREN

Medicinal products should not normally be tested in children until complete animal studies have been performed. These would include pharmacology, pharmacokinetics, acute and chronic toxicity, carcinogenicity and mutagenicity and reproduction studies (especially F1 and F2 generations). Studies in young animals may be considered useful in assessing disorders of development provided suitable validated study models are available. The adult experience of dose/effect relationships will provide a framework for dose titration and ADR monitoring in children.

6. PRESENTATION OF CLINICAL TRIALS IN CHILDREN TO COMPETENT AUTHORITIES

Data should be generated before marketing authorisation not only when a medicinal product to be used wholly or mainly in children but also for reasons of public health when:

- a) a new medicinal product is likely to be used in children because of its uniqueness (a novel therapeutic effect which is particularly applicable to a paediatric disease or a convenient dosage form);
- b) a medicinal product represents a major therapeutic advance and is likely to be used in children.

In other circumstances the medicinal product should be contra-indicated for children until further data are available after initial marketing authorisation has been granted.

7. POST MARKETING EXPERIENCE

Medicinal products which are used in children should undergo post-marketing surveillance. In this way adverse effects and information on efficacy will enable the dosage schedule and data sheets to be updated early in the lifetime of the medicinal products.