Research in Children

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The Centre for Bioethics and Patient Advocacy has been taking part in the European Forum for Good Clinical Practice (EFGCP)'s formulation of guidelines for implementing Directive 2001/20/EC[1] relating to good clinical practice in the conduct of clinical trials on human subjects. The document produced by this group focused on clinical trials in children and their protection thereof. As clinical trials become more important and common, a harmonization of the application of this directive across Europe was deemed important.

"Children are not small adults and there is a need to carry out specific trials that cannot be performed in adults."[2] Ethics committees need paediatric expertise as the lack of competence of children to give informed consent renders this group a vulnerable population. In particular parents are prone to accept their children participating in a trial upon the suggestion of the health care team. The lack of legal ability to consent has therefore also implications on the design, analysis and the choice of comparators used in trials. There is a need for clinical trials in children, especially because many drugs given to them are off-label. Moreover trials may be specific to this population, such as vaccinations.

The Declaration of Helsinki states that, "When a subject deemed legally incompetent, such as a minor child, is able to give assent to decision about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative."[3] This implies that enough information must be given to the child by an experienced professional, which the child is able to assimilate and understand. Article 4 of the Clinical Trials Directive stipulates therefore "the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principle investigator."[2]

As the child however is only capable of giving assent and not informed consent, one still needs to follow the five conditions[4,5] to obtain valid consent from the legal representative of the child. Sufficient time to consider the risks and benefits should be allowed for.[2] The document divides children into three age groups. Those under three years of age cannot give realistic assent whilst those over three are thought to understand some form of altruism. As the child gets older, children may be able to understand and evaluate the risks and benefits of the research, and their expression must therefore be taken into account. The third group, adolescents, proves most difficult. Sometimes there can be situations in which confidentiality is at stake – some EU states advice discretion and professional secrecy vis-sa-vis parents when dealing with this group. Obtaining consent from parents becomes difficult, if legally required, when assent is available form the adolescent, who is technically still considered a child under the legal guardianship of the parents. Conversely, "when the child is legally emancipated, i.e. ceases to be a minor, informed consent must be sought directly from the individual and as soon as possible".[2]

The Clinical Trials Directive requires the need for ethics committees to have paediatric expertise to give advice in the clinical, ethical and psychosocial problems in the field of paediatrics, which differ of course from the usual clinical trials in adults. This may be a paediatrician experienced in paediatric research and trials, but also a paediatric pharmacologist, paediatric nurse, paediatric ethicist or psychologist. If the ethics committee is not in charge of scientific review according to national law, it should make sure that adequate peer review by experts in the field has taken place – for example that the trial uses age-appropriate formulations of the medicinal product, or that appropriate amounts of blood are drawn, where this is necessary, considering that the volume of blood to be drawn is over and above that for the normal hospital stay. An amount not more that 1.2 ml has been suggested for children under three, especially babies.

Equipoise is important when considering a control group or the use of a placebo. The physician must be morally certain that the child is not better off not participating in the trial. Equipoise may be waived however when the trial does not involve control groups, for example post-marketing surveillance studies. It has also been suggested that research on certain drugs, following of course the scientific advice given by the professionals mentioned, should be offered only on premises where appropriate "rescue treatment and escape procedures" are available, should a serious harm occur.[2]

Of course an obvious requirement is that physical and emotional pain should be prevented as much as possible. To do this however requires appropriate monitoring on a regular basis according to guidelines and validated scales, particularly in pre-term, newborn and other children who cannot express themselves. Effective treatment in relation to the intensity of pain should be administered and reviewed regularly. Repeated blood sampling and the insertion of indwelling catheters are all sources of pain, and available pharmacokinetic data from population studies may reduce the number of samples in each child.

Risk assessment is crucial when assessing trials. In children particularly, besides the physical risks, one must consider the psychological or social risks, which may be immediate or delayed and which may vary according to age. Absenteeism from school may be a small issue to the health care team, but may have a large impact over a stretched period of time. It is often the case that the research is spread over the availability of the research team and not of the child's timetable. Ethics committees may intervene when it is deemed that the particular age group

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may be adversely affected, and that appropriate arrangements, such as the use of holidays, are used to bring children to the facilities, unless one is dealing with hospitalised children. It is all too easy to instruct parents that they must then continue to bring in the child once a week (when this may not have been adequately expressed in the informed consent process). Parents are usually the first to express concern about how much time is lost from school.

However the risk-benefit analysis may evolve over time, especially where the safety of the drug is concerned, and this must be continuous evaluated, with the provision of being able to stop the study if necessary. There are various protocols and tables of assessing what are minimal risks, and which are major ones. These must be presented by the trial sponsors and need to be evaluated by the Ethics Committee, which usually tries to ascertain that risks are minimal as well as the burden, and that the research has the aim of providing significant improvements in the scientific understanding of the condition or disease, which are able to provide benefit to the participant of the trial and other persons of the same age category.

More tricky are phase one trials, in which healthy volunteers are used. Healthy children must be used in order to understand the pharmacokinetics and pharmacodynamics of a drug, without the interference of the disease process. Phase one involves small numbers, usually in the order of tens; but still, assessing and imparting information of risk may be more difficult, unless one produces prior evidence of adult studies, or at least animal studies. This may not be necessary where the aim is to find age-appropriate dosages or for trials for vaccines. Whenever possible, it is suggested that older children should be considered for inclusion before younger ones, although the document[2] does not give particular reasons for this, other than the impression that the younger the child, the more vulnerable they are, and probably the more prone to risks. This may reduce the impact on future tests on younger children.

Finally the directive admonishes researchers performing research in non-EU countries, to strictly follow the same guidelines and GCP standards that are required within the EU. Indeed this is not only about patient rights, but at the end of the day, also about the scientific validity of the trial, for research which is not up to Good Clinical Practice standards has been found not to be scientifically valid.

References

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