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Recommendations on ethical issues on medicine for parents

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2. Abstract

In the framework of *TEDDY-NoE* activities in the field of Ethics and in collaboration with RESPECT (Relating Expectations and Needs to the Participation and Empowerment of Children in Clinical Trials – project funded under EU FP7) it has been demonstrated that it is important to provide parents with recommendations aimed at growing awareness on clinical research issues and at empowering and motivating participants (children) in future clinical research. This could lead to more valid and reliable medicines for children as envisaged by the European Paediatric Regulation 1901/2006/EC.

In particular, it is important:

- To let parents to acquire competencies and awareness on critical issues related to clinical trials
- To empower the role of parents in decision process in order to favour the participation of children in clinical trials
- To increase the role of parents in defending rights, safety and well-being of children involved in clinical research

3. Content: Recommendations

3.1. Background

The European Pediatric Regulation lays down rules to facilitate development and availability of medicines used in children and to ensure that the medicines are of high quality, can be administered in a safe and effective way and paediatric studies are ethically performed.

In order to improve parents' awareness on paediatric clinical research and to empower and motivate participants (children) in future clinical research, their involvement should be encouraged.

TEDDYNoE "Survey on ethical and legal frameworks existing in Europe for paediatric clinical trials" emphasized that many differences exist in Europe related to the protection of minors involved in clinical trials across Europe due to the Directive 2001/20/EC implementation process as well as to a lack of coordination. These differences may lead to some inequalities in the protection of minors across Europe.

Furthermore, according to RESPECT preliminary results it should be underlined that:

- patients' (children) and parents' comprehension of information provided to potential participants of clinical trials is often limited. Treatment and research appear inseparable to parents of children participating in a clinical trial.
- In the decision-making process, parents potentially fail to grasp the distinction between the imperatives of clinical research and of ordinary treatment. This "therapeutic misconception" may lead to higher participation rates because the parents or patients sign the consent forms with an only modest appreciation of risks and disadvantages of participation.
- Some parents can perceive time pressure to start the treatment as soon as possible after the diagnosis and this can lead to a lack of time to discuss all the possibilities with the physician .
- New ways to fulfill the special needs of young patients and their families in the situation of considering participation in a clinical trial are needed. Strategies to promote question-asking are needed to include the young patient in the decision-making process.
- Beyond the quality of communication, more attention should be paid to the emotional state and stress families may experience in the situation of disclosure of a diagnosis, frequently associated with the consent procedure
- Addressing available psychological knowledge might be helpful in understanding the needs of children and parents and, based on this, improving participation levels and enhancing the family's experience of the clinical trial itself.

In the light of these findings, the main goals to achieve are:

- To let parents to acquire competencies and awareness on critical issues related to clinical trials
- To empower the role of parents in decision process in order to favour the participation of children in clinical trials
- To increase the role of parents in defending rights, safety and well-being of children involved in clinical research

3.2. Recommendations

TEDDY recommends parents:

- 1) to increase general knowledge on clinical trials by consulting relevant and reliable documents and data (e.g. make reference to the European Ethical recommendations - Eudralex vol.10/2008 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/ethical_considerations.pdf as well as to national legislation that you can/should obtain by your doctor/investigator)
- 2) To verify their knowledge and degree of comprehension on the most relevant concepts as summarized in the annexed table
- 3) To be aware that, as legal representative of their child, they have to provide their authorization for allowing him to participate in a clinical trial. To this aim, they should pay special attention to the following items:
 - Your child has been requested to participate in a clinical study that is different from medical care
 - The protocol related to the study your child is requested to participate in has been approved by an Ethics committee
 - Appropriate paediatric expertise is available in the site where clinical trial is carried out
 - You have received an information/consent form including all the relevant information on the following aspects:
 - the objectives, the nature, extent and duration of the procedures used, in particular, details of any burden imposed by the research project;
 - available preventive, diagnostic and therapeutic procedures;
 - the arrangements for responding to adverse events or the concerns of research participants;
 - arrangements to ensure respect for private life and ensure the confidentiality of personal data;
 - arrangements to ensure that child will know any information collected on his/her health
 - arrangements for access to information relevant to the participant arising from the research and to its overall results;
 - arrangements for fair compensation in the case of damage;
 - any foreseen potential further uses, including commercial uses, of the research results, data or biological materials;
 - any medical procedures used to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage (both the risk threshold and the degree of distress have to be specially defined and constantly monitored);

All this information should provide them with a global and comprehensive understanding of the benefits and risks for their child. The same level of care and information should be maintained during treatment or investigations.

- 4) To be aware that their child is entitled to participate in the decision process to take part in clinical trials, receiving information and providing assent (favorable opinion).

To this aim, parents (legal representatives) have to verify that child receive a comprehensive information, in a language and wording appropriate to age, psychological and intellectual maturity, on the following aspects:

- the objectives, the nature, extent and duration of the procedures involved, in particular, details of any burden imposed by the project;
- available preventive, diagnostic and therapeutic procedures;
- the arrangements for responding to adverse events or the concerns of research participants;
- arrangements to ensure respect for private life and ensure the confidentiality of personal data;
- arrangements to ensure that child will know any information collected on his/her health arrangements for access to information relevant to the participant arising from the research and to its overall results;
- arrangements for fair compensation in the case of damage;
- any foreseen potential further uses, including commercial uses, of the research results, data or biological materials;
- any medical procedures used to minimise pain, discomfort,
- fear and any other foreseeable risk in relation to the disease and developmental stage (both the risk threshold and the degree of distress have to be specially defined and constantly monitored);

The same level of care and information should be maintained during treatment or investigations.

They have to be sure that, on the basis of this information, their child is totally aware of the nature of procedures and possible pain and discomforts arising from the trial.

- 5) To be aware that they are not obliged to accept that their child is involved in clinical research. Furthermore, they can refuse to authorize their child or withdrawn their consent to participation in research at any time without leading to any liability and/or to any form of discrimination against the child concerned, in particular regarding the right to medical care.
- 6) To be aware that their child can refuse to participate in clinical research or to continue to be involved at any time without detriment or medical care interruption
- 7) In case of different opinion between them and their child every effort should be done to understand and respect the opinion of the child. Strong and definitive objections from the child should be respected.

- 8) To be aware that there must be not inducement either for them and/or their child to enter in a clinical trial
- 9) To be aware that they have the right to access to the global results of research after it is completed
- 10) To verify the terms of the insurance contract subscribed to cover damages arising from the trial. Be careful that information/consent form should contain no words that would absolve an investigator [or sponsor] from responsibility in the case of accidental injury, or that would imply that subjects would waive their right to seek compensation for impairment, disability or handicap arising from the participation in the research. They should pay special attention to waivers of liability in the insurance contract, in particular with respect generally to long term effects on the development of the child included in research.

4. Receivers of the document

Public document.

5. References to other documents

Annex 1 - Definitions

Topic	Definitions/concepts to take in mind
Child -minor	Child in the context of clinical trial is intended as minor. The term minor will be used and it applies to all individuals from birth until the legal age of adulthood (usually 18 years and above rarely 16 years according to national legislation)
Clinical trial definition to distinguish it from medical care	"Clinical trial": any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy
Conditions to undertake clinical trial on children	<p>A clinical trial may be undertaken only if, in particular:</p> <p>(a) the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual child and other present and future children. A clinical trial may be initiated only if the Ethics Committee and/or the competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored;</p> <p>(b) some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors</p> <p>(b) the legal representative (parents) of the child has had the opportunity, in a prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the trial, and the conditions under which it is to be conducted and has also been informed of his right to withdraw from the trial at any time;</p> <p>(c) the rights of the child to physical and mental integrity, to privacy and to the protection of the data concerning him are safeguarded;</p> <p>(d) the legal representative of the child has given his written consent (authorisation) after being informed of the nature, significance, implications and risks of the clinical trial; this consent (authorisation) must represent the minor's presumed will and may be revoked at any time without detriment to the child;</p> <p>(e) the minor has received information according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits;</p> <p>(f) refusal of the child shall be respected; the child may without any resulting detriment withdraw from the clinical trial at any time by revoking his informed assent;</p> <p>(g) provision has been made for insurance or indemnity to cover damages arising from the clinical trial</p> <p>(h) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored;</p> <p>3. The medical care given to, and medical decisions made on</p>

Topic	Definitions/concepts to take in mind
	<p>behalf of, child shall be the responsibility of an appropriately qualified doctor or, where appropriate, of a qualified dentist.</p> <p>4. Parents and children shall be provided with a contact point where he may obtain further information</p>
Ethics committee definition	<p>"Ethics committee" is an independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent</p>
Paediatric expertise of Ethics committees	<p>Ethics committees shall include paediatric expertise when reviewing protocols involving paediatric population. Paediatric expertise may be defined on the basis of education, training and experience on the various aspects of child development, ethics and psychosocial aspects as well as on the basis of the experience in paediatric care and direct experience of clinical trials with children. Expertise used should be documented and recorded by the ethics committee. If this expertise cannot be found in one individual, two or more paediatric experts could contribute to the expertise needed.</p>
Appointment of ad hoc rapporteurs	<p>Paediatric protocols have to be endorsed by the ethics committee including paediatric experts (who could be permanent members) or after taking advice in clinical, ethical and psychological problems in the field of paediatrics.</p>
Description of the project including healthy volunteers	<p>In principle, healthy children should not be enrolled as healthy volunteers, because they cannot consent. Exceptions could be e.g. trials in children with intermittent diseases, or prevention trials (including immunogenicity studies that include the target population likely to benefit) or where healthy children participate in palatability testing such as swill and spit taste testing for a new flavoured medicine. Whenever possible the older age groups should be considered for inclusion before the younger ones. Anyway proof of concept should first be obtained in relevant animal models and/or adults whenever possible".</p>
Placebo controlled study	<p>A method of investigation of drugs in which an inactive substance (the placebo) is given to one group of participants, while the drug being tested is given to another group. The results obtained in the two groups are then compared to see if the investigational treatment is effective in treating the condition.</p>
Use of placebo	<p>Placebo is permissible only where there are no methods of proven effectiveness and safety, or where withdrawal or withholding of such methods does not present an unacceptable risk or burden. Extreme care must be taken to avoid abuse of placebo option. Use of placebo in children has to be more restricted than in adults. Other trial designs should be considered if appropriate. As many medicines used in children have not been fully assessed and authorised, the choice of active control products should be discussed thoroughly. Medicinal products not having a marketing authorisation may be considerable suitable as controls if they represent evidence-based standard of care.</p>