Funded under
VI Framework Programme

Project Number: LSHB-CT-2005-005216

TEDDY

TASK-FORCE IN EUROPE FOR DRUG DEVELOPMENT FOR THE YOUNG

INSTRUMENT: NETWORK OF EXCELLENCE

THEMATIC PRIORITY: LIFE SCIENCES, GENOMICS AND BIOTECHNOLOGY FOR HEALTH

D087

Recommendations on ethical issues on medicine for children targeted to children and young people

TD-D087-Recomm_ethical_issues_medicine_children.doc

DUE DATE OF DELIVERABLE: 31 MAY 2010
ACTUAL SUBMISSION DATE: 31 MAY 2010
ORGANISATION NAME OF LEAD CONTRACTOR FOR THIS DELIVERABLE: AZIENDA OSPEDALIERA DI PADOVA (AOPD)

START DATE OF PROJECT:	01 JUNE 2005
DURATION:	5 YEARS
PROJECT COORDINATOR NAME:	ADRIANA CECI
PROJECT COORDINATOR ORGANISATION NAME:	CONSORZIO PER VALUTAZIONI BIOLOGICHE E FARMACOLOGICHE (CVBF)

REVISION DATE:	DRAFT	FINAL
		31 MAY 2010

PROJECT CO-FUNDED BY THE EUROPEAN COMMISSION WITHIN THE SIXTH FRAMEWORK PROGRAMME (2002-2006)		
DISSEMINATION LEVEL		
PU	PUBLIC	**X**
PP	RESTRICTED TO OTHER PROGRAMME PARTICIPANTS (INCLUDING THE COMMISSION SERVICES)	
RE	RESTRICTED TO A GROUP SPECIFIED BY THE CONSORTIUM (INCLUDING THE COMMISSION SERVICES)	
CO	CONFIDENTIAL, ONLY FOR MEMBERS OF THE CONSORTIUM (INCLUDING THE COMMISSION SERVICES)	

Document Profile					
Code		**Title**		**Visibility**	
TD-087		Recommendations on ethical issues on medicine for children targeted to children and young people		Public	
Aim of the document				**Receivers**	
To provide children with recommendations in order to favour the growing of awareness of clinical research issues in order to empower and motivate children in future clinical research				Scientific Society ☐ Health Professionals ☐ Public ☐ Industry ☐ Regulatory Agencies ☐ TEDDY NoE ☒ European Commission ☒	
Key Words (separated by commas)					
Ethics, clinical research, paediatrics					
Acknowledgements (Enter data source: the organization or publication. < 250 characters)					
Pertinent WP		**Reference activity**			
7		A059-Produce recommendations on Ethical issues on Medicine for children targeted to children and young people			
Drafted by	**Date**	**Submitted by**	**Date**	**Approved by**	**Date**
Annagrazia Altavilla	31/05/10	C. Giaquinto	31/05/10	Objectives Coordinators	
Approved by	**Date**	**Approved by**	**Date**	**Approved by**	**Date**
Executive Board		Ethics Advisory Group		Network Governing Council	

Index

1. Authors 4
2. Abstract 4
3. Content: Recommendations 5
3.1. Background 5
3.2. Recommendations 6
4. Receivers of the document 9
5. References to other documents 9
Annex 1 - Definitions 10

1. Authors

Table 1: list of authors

Name	Institution
Annagrazia Altavilla	TEDDYNoe – WP7 (Ethics) - Coordinator of TEDDY activities in the field of Ethics -Espace Ethique Méditerranéen- E.A. 3782. Member of PDCO (EMA)
Cristina Manfredi	CVBF Pavia
Carlo Giaquinto	AOPD, Italy, WP7 Leader
Adriana Ceci	TEDDY Coordinator CVBF, Pavia, Member of PDCO * on behalf of TEDDY-Task Force in Europe for Drug Development in the Young

2. Abstract

In the framework of TEDDYNoE 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 children 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 children to acquire competencies and awareness on critical issues related to clinical trials
- To empower the role of children in decision process in order to favour their participation in clinical trials

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 children awareness on paediatric clinical research and to empower and motivate them to participate in future clinical research, their involvement should be encouraged.

RESPECT preliminary results pointed out 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.

According to EU Ethical recommendations (eudralex vol.10/2008), for children from birth to 3 years of age it is not possible to obtain assent and understanding of research is not expected. From 3 years of age there is the emergent capacity to agree. Children from the age of 3-4 years can understand benefits and some expression of altruism. From the age of 9, children may be able to understand benefits and risks of research but are less able to understand conflicting of abstract information. It is the major importance to inform the child and obtain assent, preferably in writing, when the child is of "school age" (about 6-7 years old) i.e. able to read and write and to keep track of such assent. Adolescents belong to the paediatric group, although they have the capacity to make adult decisions in many other areas of life. Most guidelines and publications recognise

that adolescents are, under certain circumstances, able to make independent judgements. In case of difference of opinion between the child and the parents/legal representative, every effort should be made to understand and respect differences of opinion between the child and his/her parents or legal representative. Strong and definitive objections from the child should be respected.

These guidelines have to be followed taking into account that the individual capacity is also linked to developing cognition and previous life/disease experiences.

Furthermore, on the basis of TEDDYNoE activities it has been pointed out that some countries implementing Directive 2001/20/EC 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 consent of 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".

3.2. Recommendations

In the light of the above reported findings, the main objectives to be achieved are:

- To let children to acquire competencies and awareness on critical issues related to clinical trials
- To empower the role of children in decision process in order to favour their participation in clinical trials

To this aim TEDDY recommends children from age-school:

1) To verify their knowledge and degree of comprehension on the most relevant concepts summarized in the table annexed with the help of their parents/doctors/educators
2) To be aware that parents/legal representative have to provide authorization for allowing them to participate in a clinical trial. To this aim, they should pay special attention to the following items:
    - You are been requested to participate in a clinical study that is different from medical care
    - The protocol related to the study you are 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
    - Parents/legal representatives 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 involved, 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 parents/legal representatives with a global and comprehensive understanding of the benefits and risks for you. The same level of care and information should be maintained during treatment or investigations.

3) To be aware that you are entitled to participate in the decision process to take part in clinical trials, receiving information from doctors/investigators 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:

   a) the objectives, the nature, extent and duration of the procedures involved, 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;
   b) arrangements to ensure respect for private life and ensure the confidentiality of personal data;
   c) arrangements to ensure that child will know any information collected on his/her health
   d) 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 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, they are totally aware of the nature of procedures and possible pain and discomforts arising from the trial.

4) To be aware that they are not obliged to accept that they are involved in clinical research. Furthermore, they can refuse or withdrawn their assent to participation in research at any time without leading to any liability and/or to any form of discrimination m t, in particular regarding the right to medical care.
5) In case of different opinion between them and their parents (legal representatives) every effort should be done to understand and respect their opinion. Their strong and definitive objections should be respected.
6) To be aware that there must be not inducement either for their parents (legal representatives) and/or them to enter in a clinical trial
7) To be aware that they have the right to access to the global results of research after it is completed
8) They can ask for psychological support and/or for having a reference person to clarify their doubts and /or to help them.

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	A clinical trial may be undertaken only if, in particular: (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; (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 (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; (c) the rights of the child to physical and mental integrity, to privacy and to the protection of the data concerning him are safeguarded; (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; (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; (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; (g) provision has been made for insurance or indemnity to cover damages arising from the clinical trial (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; 3. The medical care given to, and medical decisions made on

Topic	Definitions/concepts to take in mind
	behalf of, child shall be the responsibility of an appropriately qualified doctor or, where appropriate, of a qualified dentist. 4. Parents and children shall be provided with a contact point where he may obtain further information
Ethics committee definition	"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
Paediatric expertise of Ethics committees	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 paediatrc experts could contribute to the expertise needed.
Appointment of ad hoc rapporteurs	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.
Description of the project including healthy voluntarees	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".
Placebo controlled study	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.
Use of placebo	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.