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Children's views on their involvement in clinical research

H Chappuy[1,2], F Doz[3], S Blanche[4], JC Gentet[5], JM Tréluyer[6].

[1] Département d'Urgences Pédiatriques, Hôpital Necker Enfants Malades, Paris, France

[2] Laboratoire d'Ethique Médicale Université René Descartes, Paris, France

[3] Département d'Oncologie pédiatrique, Institut Curie, Paris, France

[4] Unité d'Immunologie-Hématologie, Hôpital Necker Enfants Malades, Paris, France

[5] Oncologie pédiatrique, Hôpital La Timone, Marseille, France

[6] Pharmacologie Faculté et Université Paris Descartes, Paris, France EA 3620

II.1. Les objectifs de l'étude

Les objectifs principaux de notre travail étaient :

- D'étudier la compréhension par les enfants de l'information reçue lors du recueil du consentement
- De chercher les éléments qui pouvaient prédire une bonne compréhension

Les objectifs secondaires de notre travail étaient de recueillir:

- Les connaissances générales sur la recherche et les essais cliniques par les enfants
- Le jugement par les enfants de la qualité de l'information reçue
- Et s'ils avaient participé à la décision finale

II.2. La méthodologie de l'étude

Ce travail a été réalisé selon la même méthodologie que le précédent dans les 3 mêmes services d'oncologie et d'hématologie pédiatriques : Institut Curie, Hôpital Necker-Enfants Malades et Hôpital La Timone.

Les enfants de plus de 7 ans dont nous avions rencontré les parents dans les centres participants, étaient vus séparément en entretien semi-directif. Nous ne rencontrions pas les enfants dont les parents refusaient qu'ils répondent à nos questions.

Les consignes pour les enfants étaient les suivantes :

« Je te remercie d'avoir accepté de répondre à mes questions. Je m'intéresse aux enfants qui ont participé à un protocole de recherche. C'est ton point de vue d'enfant qui m'intéresse. Ce que tu me diras ne sera pas répété dans le service et ton nom n'apparaîtra pas dans mon travail. Cela ne changera pas ce qu'on te fait pour te soigner. Si tu es d'accord, je vais enregistrer notre conversation ce qui m'évitera de prendre des notes, pour faciliter notre entretien. Je vais te poser les mêmes questions que celles de tes parents, tu peux me répondre « je ne sais pas » ou ne pas me répondre».

Les entretiens avaient lieu sur place, étaient enregistrés et retranscrits intégralement, « mot pour mot ». Chaque question leur était expliquée (si besoin), dans un langage approprié à l'âge de l'enfant, sans avoir une attitude coercitive. Le canevas d'entretien était identique à

celui des parents mais était exprimé avec des mots plus simples (cf. Annexe1). Toutefois, concernant la décision, les questions étaient les suivantes :

- *« As-t-on demandé ton avis pour la décision? Pourquoi ? Est-ce pour toi indispensable? »*
- *« D'après toi, qui a pris la décision finale ? »*
- *« D'après toi, la relation que tes parents et toi avez avec le médecin qui vous propose le protocole influe-t-elle sur la décision ? Qu'attends-tu du médecin ? »*
- *« A partir de quel âge penses tu qu'un enfant puisse prendre la décision de participer (ou non) à un protocole de recherche ? »*

II.3. Résultats résumés

Nous avons réalisé 29 entretiens. Les enfants étaient âgés de 8,5 ans à 18 ans (13.6 ± 2.8 années). Onze enfants (38%) ne savaient pas qu'ils avaient participé à un protocole de recherche. Les items les mieux compris par les enfants étaient le but de l'étude (n=18, 62%), les risques (n=17, 58%), le bénéfice individuel possible (n=18, 62 %), le bénéfice éventuel pour les autres enfants (n=17, 58%). Les items qui étaient moins bien compris étaient les procédures (n=5, 17%), la possibilité d'alternative thérapeutique (n=9, 31%), la durée de participation (n=6, 21%), le droit de se retirer de l'étude à tout moment (n=6, 21%) et le volontariat (n=6, 21%). Seize enfants (55%) pensaient que l'information reçue était adéquate. La compréhension était en corrélation avec l'âge et le score moyen était plus élevé chez les enfants de plus de 14 ans comparés aux enfants de moins de 14 ans. Seize enfants (55%) répondaient qu'ils avaient participé à la décision mais tous (à l'exception de 2) disaient que c'étaient leurs parents qui avaient pris la décision finale.

II. 4. Article 2

Children's views on their involvement in clinical research.

Hélène Chappuy[1,3], MD, François Doz[4], MD, Stéphane Blanche[3,5], MD PhD, Jean-Claude Gentet[6], MD, , MD PhD, Jean-Marc Tréluyer[2,3], MD PhD.

Short title : Children in pediatric research

1: Département d'Urgences Pédiatriques, Hôpital Necker Enfants Malades, Assistance Publique Hopitaux de Paris et Laboratoire d'Ethique Médicale Université René Descartes Paris France

2: Pharmacologie Clinique, Hôpital Cochin Saint-Vincent-de-Paul Assistance Publique Faculté de Médecine René Descartes Paris, France

3 EA 3620 Faculté et Université René Descartes Paris France

4:. Département d'Oncologie pédiatrique, Institut Curie, Paris, France

5: Unité d'Immunologie-Hématologie, Hôpital Necker-Enfants Malades, Faculté de Médecine René Descartes Paris, France

6: Oncologie pédiatrique, Hôpital La Timone,Faculté de Médecine Aix Marseille, Marseille, France

Corresponding author

Hélène Chappuy

Département d'Urgences pédiatriques

Hôpital Necker Enfants Malades

149 rue de Sèvres 75743 PARIS Cedex 15 FRANCE

Telephone number 33144494370 FAX Number 33144494299

helene.chappuy@nck.aphp.fr

Abstract.

Objective : To examine the level of children's understanding of informed consent in clinical trials and factors that may influence these processes.

Design : Twenty nine children who were included in clinical trials for treatment of cancer or HIV, were offered the possibility to complete an semidirective interview, with parental permission.

Methods : Children's understanding was measured by a score 0 to 9 including items required to obtain a valid consent according to French and European legislation.

Results : Children were 8.5 to 18 years old (13.6 ± 2.8 years). Items that were best understood by children were the aims of the study (n=18, 62%), the risks (n=17, 58%), the potential self benefits (n=18, 62 %), the potential benefits to other children (n=17, 58%). Items that were least understood were the procedures (n=5, 17%), the possibility of alternative treatments (n=9, 31%), the duration of participation (n=6, 21%), the right to withdraw (n=6, 21%) and willingness (n=6, 21%). Sixteen children (55%) thought that the information given was adequate. Understanding was significantly correlated with child's age (r=0.65; p=0.0001) and the mean score was higher in children above 14 years compared to children below 14 years (4.4 ± 2.4, n=14 vs. 2.6 ± 2.6, n=15, p<0.05). The mean score was also higher in children when informed consent was sought some time after the diagnosis rather than at the same time (score: 4.14± 2.59 n=21 vs. 1.87±2.03 n=8; p=0.03). Understanding was not influenced by the impression of clearness of the pointed out informations (score: 3.6 ± 2.6 n= 14 vs. 3.5 ± 2.7 n= 15; p=0.91)**.** There is no relationship between parents and children understanding (r=0,02 p=98)

Conclusion : Children have an incomplete understanding of the elements included in the informed consent forms. Understanding is related to age and time of informed consent but not parents understanding.

Keywords: children, clinical research, informed consent, understanding.

INTRODUCTION

The need for research involving children is now recognized and action has been taken at the federal level in USA to address both the need for pediatric research and the protection of the welfare and rights of children as research subjects **(1).** More recently a EU Regulation on Medicinal Products in children has been prepared and adopted by EU Parliament **(2)**. Advances in the area of human protection, part of which is the process of informed consent in pediatric trials, do not evolve at the same pace as do advances in science. This process is further complicated in paediatric trials as a third party is involved. The "geometry" of paediatric ethics is best understood as a triangle with the child on the top and the parent(s) and clinician-investigator at the base to act as support. Parents are considered as the appropriate decision-makers for their child's participation in research; however, US and european legislation recognize the child's right to autonomy and self-determination and the child, if deemed able to do so, must give his or her assent (affirmative agreement) **(3, 4)**. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research suggests that a child aged 7 years with normal cognition, is capable of providing meaningful assent **(5, 6)**. In France, the child must be informed according to his maturity and cognitive abilities**(7, 8)**. Little attention has been focused on the minor's perspective regarding participation to research. We have previously shown that there was an apparent discrepancy between parents' evaluation of the adequacy of the information delivered and hetero-evaluation of their understanding. The majority of parents preferred that the physician take as much responsibility as possible in the decision making process **(9)**. And what about their children? The present study sought to examine the level of children's understanding of the informed consent in a HIV or oncology clinical trials and factors that may influence their decision. Our objective was also to assess how children evaluated this important issue.

METHODS

The study population included children treated for either a cancer or an HIV infection and who were recruited in clinical trials. In a previous study, we have examined the parents' understanding of informed consent (n=68) **(9)**. All the children of these families were included in this present study. Children under the age of 5 were excluded. An Institutional Review Board approved all these clinical trials. The present study was conducted during a six month period in three hospitals in France where children were: Curie Institute (Paris), Necker Enfants Malades Hospital (Paris) and Timone Hospital (Marseille).

Regardless of whether the parents had consented or not to allow their child to participate in a clinical trial, children were invited by their referent doctor to complete a semi directive interview with parental permission. Children who agreed to participate were interviewed by a paediatrician trained in clinical research and ethical aspects of clinical research, either during the child's inpatient admission in the pediatric hospital or in the outpatient clinic. This choice was made in order to both minimize parents and children' travel and maximize participation. The interviewer was the same during the whole study and was involved neither in the care of the child nor in the clinical trial performed in the three hospitals. At the beginning of the interview, children were informed that their answers would be kept confidential and would not affect their care in any way. . The interview was organized in a semi-structured manner and the wording of the questions was adapted to be age appropriate. The interviewer was allowed to clarify questions and prompt the children for additional information about the interview's questions The interview was audiotaped after children's agreement.

At the beginning of the interview, children were asked about the information they received from the investigator ("Who gave this information to you: doctor, parents, nurse?", "I would like to know how well you think the study was explained to you: great, too much, not enough or you don't know?", "According to you, who should give this information?").

The interview was designed to determine the children's understanding of 9 items required to be included in the informed consent document (study purpose, methodology of the protocol, risks, direct and indirect potential benefits, the right to withdraw, duration of participation, possibility of alternative treatments, volontariness) **(7, 8, 10)**. The children's levels of understanding of these individual items were scored for each item after the interview comparing the written transcription of the interview to the informed consent forms signed by the children and the parents. Scores 0 or 1 were assigned for each item: score 0 was assigned to the item if the children was unable to respond to the question and score 1 was assigned to the item if the response was consistent with the informed consent signed by the parents and the children. A global score was calculated ranging from 0 to 9 which was the sum of the scores for each item as previously described **(9).**

The items and the corresponding questions during the interview were as follows **(11)**:

- study purpose (Can you tell me why this study is being done?)
- protocol design and procedures (What is going to happen to you in this study?)
- risks (What are the possible bad things that might have happened to you by being in the study?)
- direct benefits (What are the possible good things that might have happened to you by being in the study?)
- indirect benefits (What are the possible good things that might have happened to other kids by you being in the study?)
- the right to withdraw (Would it have been OK to stop the study if you change your mind about being in it?)
- duration of participation (Approximately how long have you been participating in the study?) This item was scored 1 if the difference between the interview and the protocol was less than 30% of the exact response.

- alternative treatments or procedures (Do you know what would have been done to you differently if you had decided that you did not want to be in the study?)
- willingness (Did you have a choice of whether or not to be in the study?)

Information was elicited as to whether they had given their point of view, the reason(s) for his (her) participation and who made the decision. The corresponding questions during the interview were as follows:

-"Did you participate in the decision making process?"
- "Who made the decision of whether you enter the clinical study or not?"
-"Regarding the relationship with the doctor asking you what was important for you?"

The following items were also recorded: type of disease (cancer or HIV), type of clinical trial (interventional or observational), time elapsed between child's diagnosis and consent, time elapsed between consent and date of the interview, child's age, parents' geographic origin.

Statistical analysis was performed using NCSS. Descriptive statistics were calculated for sociodemographic details and children' answers. The Spearman correlation coefficient was used to measure the association between two quantitative variables. The non parametric Mann-Whitney U test was used to compare quantitative data. Data were expressed as percentages, mean ± SD. Significance was accepted at the 5% level ($p<0.05$).

RESULTS

Forty three children were approached for interview (>5 years old). Finally, 29 interviews were studied. Of the 14 children who were not interviewed, 8 had no parental permission, 1 was critically ill and 5 were not available at the time the interview was sought. The age of these children ranged from 8.5 to 18 years (13.6 ± 2.8 years). Of the 29 children interviewed, 18 (60%) were treated for an HIV infection and 11 (38%) for cancer.

Twenty seven of the children (90%) interviewed were European, the remaining 2 (7%) were African. Nineteen children (65%) had two parent-homes, 8 (27%) were single parent-homes and 2 (7%) had a legal guardian. All children interviewed had been enrolled in an interventional study including 2 (7%) in a phase I, 7 (23%) in a phase II, 6 (21%) in a phase III (randomized clinical trial) and 14 (48%) in a phase IV (post marketing) study. Child's diagnosis and consent had been explained during the same period (< 7 days) for 9 children (31%).

Understanding

Sixteen children (55%) thought that the information given was adequate, 5 (17%) thought they were not informed and 8 (28%) didn't answer this question. According to the children, information was given by the doctor (n=18, 62%), the parents (n=7, 24%), doctor and parents (n=4, 14%) and two children (7%) didn't remember. Children thought that the information must be given by the physician (n=13, 45%), physician and parents (n=8, 27%), parents alone (n=4, 14%), parents and nurse (n=1, 3%) and the nurse alone (n=1, 3%). Two children (7%) didn't answer this question.

Twenty four children (83%) understood and remembered at least one of the 9 items and 2 children (7%) aged 13.5 and 16 yr, had full understanding and recall of all the items required by the legislation to be included in the informed consent document.

Items that were best understood were the aims (n=18, 62%), the risks (n=17, 58%), the potential self benefits (n=18, 62%) and the potential benefits to other children (n=17, 58%). Items that were least understood were the procedures (n=5, 17%), the possibility of alternative treatments (n=9, 31%), the duration of the participation (n=6, 21%), their right to withdraw (n=6, 21%) and willingness (n=6, 21%) (**Figure 1**).

Several factors were found to be significantly associated with better understanding. There was a significant correlation between child's age and understanding score (r=0.65; p=0.0001)

(Figure 2). Score was higher in children above 14 years (4.4 ± 2.4 vs. 2.6±2.6; p=0.04) **(Figure 3)**. There was a significant statistical relationship for a better understanding when informed consent was sought some time after diagnosis rather than at the same time (4.14± 2.59 vs. 1.87±2.03; p=0.03). There was a trend for a better understanding when informed consent was sought for HIV infected children (3.94± 2.53 vs. 2.58±2.74; p=0.17).

Understanding was not influenced by impression of clearness of the informations obtained from investigators (3.39± 1.53 vs. 3.75±2.18; p=0.87).

Child's opinion about decision

-"Did you participate in the decision making process?" Sixteen children (55%) said that they participated in the decision: the reasons were "because I am primarily involved" (n=12) or "for better acceptance of my illness" (n=4). Thirteen children (41%) said they had not participated in the decision: their reasons alleged were "I place confidence in my parents" (n=7), "I have no choice" (n=4) or "it's too hard for me" (n=2). One 17-year-old child didn't answer this question.

-"Who made the decision of whether you enter the clinical study or not?"

In 2 cases (7%), children declared they have made the final decision: they were 16 and 18 yr old and had a guardian. Nine children (31%) declared that parents had made the decision together with the investigator, 6 (21%) let the physician decide for them and 5 (17%) made the decision alone. Eight children (28%) were unable to answer this question.

-"Regarding the relationship with the doctor asking you to participate to a study what was important for you?"

Fourteen children (48%) didn't know how to answer this question. The main requirement the children spontaneously had for accepting to participate in the study was the confidence they placed in the investigator (n=12, 41%) and his capacity to listen to them (n=4, 14%).

In the present study, all children who participated in the decision (n=16, 55%), reported that they accepted to participate because they would receive the best available treatments (n=11), or could learn more about his (her) pathology (n=5).

Except 2 children who declared they had made the final decision, others said the final decision was the parents' responsibility.

DISCUSSION

Our results show that children have a limited understanding of the elements included in the informed consent forms. There are few data regarding the children's understanding of their enrolment in clinical research. Ondrusek et al **(12)** have examined the quality of children's assent to a non-therapeutic nutritional clinical trial and Tait et al **(11)** children's understanding of the elements of disclosure for clinical anaesthesia or surgical studies. No data are available concerning chronic life threatening diseases. In our study, children had an inadequate understanding of items regarding their autonomy: willingness, freedom to withdraw and treatment alternatives. The same results were observed for parents of these children **(9)**. On the other hand, children in our study were able to understand others items like the aim, the risks, the potential self benefits and the potential benefits to other children. We can state that these items are certainly the most important elements required for the clinical trial decision making process. Better results concerning understanding were obtained in the previously published studies **(11, 12)**. When interpreting results we obtained, we must take into account that they concern high-risk diseases. As such, they may not be able to be generalized to studies involving low risk/benefit profiles.

During the first several days that follow the diagnosis of a life-threatening disease, children and their parents are very shocked and anxious, the time-lag is often very limited and their ability to understand information and take a decision decreases. Angiolillo et al **(13)** have

shown that the utilization of a staged approach to the consent process for leukaemia studies increased the parents' trust scores and that a consent process with a staged approach can help investigators obtain a more truly informed consent.

We did not evidenced any significant relationship between understanding of the parents and understanding of the children. This result could suggest that investigators should directly deliver the information to children even if parent understanding is adequate.

Understanding was influenced by age in our population of children aged above 8 and under 18. These results are consistent with the two other previously published **(11, 12)**. Tait et al showed age alone was significantly associated with understanding, particularly in children aged more than 11 yr **(11)**. In another study about the ability of children and adolescents to take informed treatment decisions, Weithorn et al **(14)** showed that 14-year-olds did not differ from adults. Nine-year-olds appeared less competent than adults did but able to participate meaningfully in personal health-care decision-making. The challenge for the investigator is to determine the age or developmental level at which assent or affirmative agreement should be sought and the age appropriateness of the disclosed information. In Canada, children aged more than 14 yr give their consent, in USA Committee on Bioethics **(15)** suggests that most children aged more than 14 yr have sufficient capacity to make decisions regarding their health care and the National Commission recommends that assent be sought for those aged more than 7 yr **(6)**.

It is possible that the beliefs about the feelings of those who have the authority would inhibit a child from withdrawing from a study. In our study, half of the decisions were made together by children and parents (according to the children). Except for 2 children who declared they had made their final own decision, others said the final decision was the parents' responsibility. Like in several other studies, we may suggest that parents have a significant influence on their child's wishes regarding participation to a study **(11, 16)**. While

it is clear that even very young children can and do express desires, it is accepted that children are unable to make independent, cognitively complex decisions for themselves. As children mature and their intellect, self-understanding, and sense of separate personhood develops, they are increasingly able to express sustained preferences that meet some tests of discernment, logic, coherence, and emerging personal value **(16).** During late childhood and preadolescence, the capacity to accept a pre-offered choice (i.e., assent) becomes evident **(15).**

In conclusion, every attempt should be made to ensure that children have sufficient information and understanding to formulate a preference for participation. A time lag between diagnosis and informed consent improves the understanding and information. The communication process should be adjusted by considering such factors as the child's age, maturity and the complexity of the medical case. It behoves the investigator to present age-appropriate disclosure in an ethically sensitive manner that is conducive to understanding.

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Figure 1: Items of the informed consent understood by children

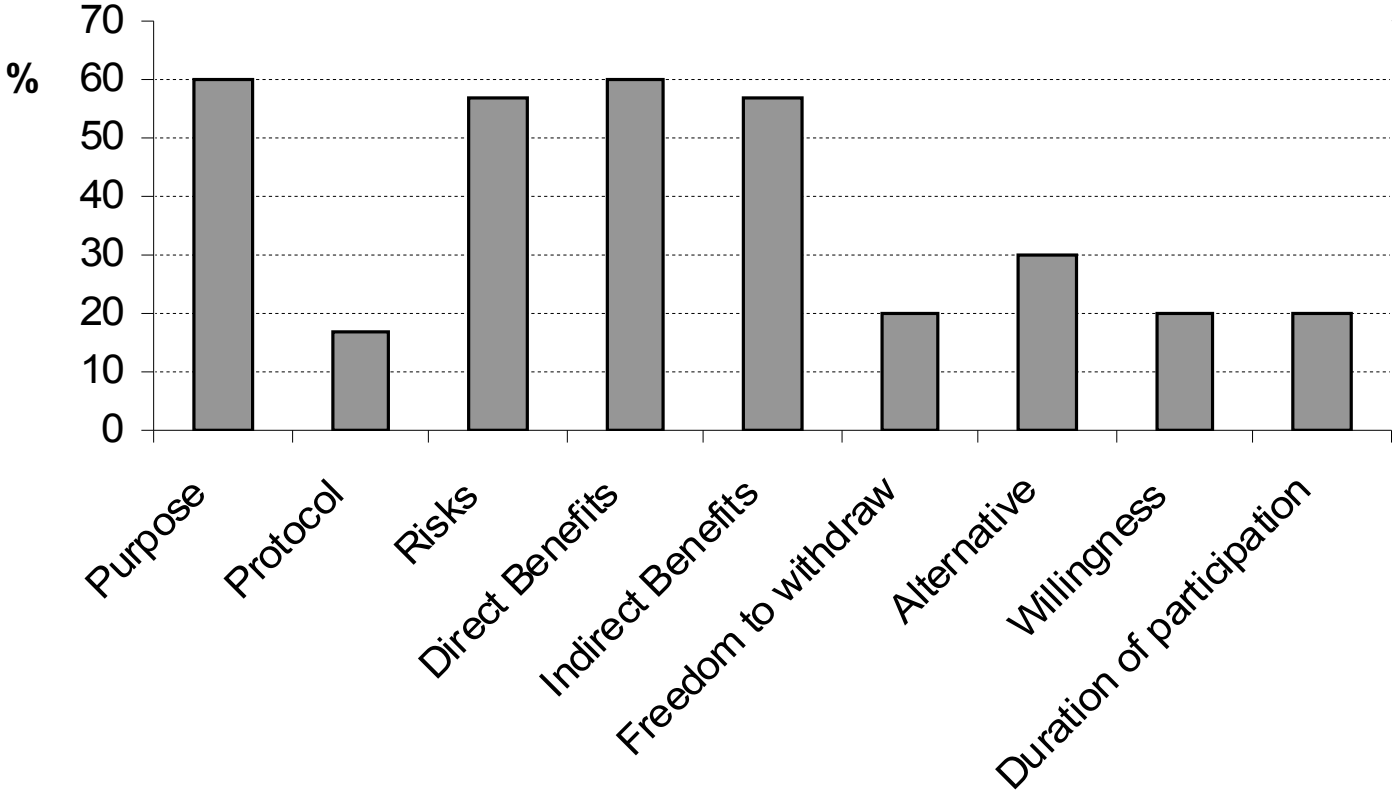

Figure 2: Relationship between child's age and child's understanding

A global score was calculated ranging from 0 to 9 which was the sum of the scores for each item (study purpose, methodology of the protocol, risks, direct and indirect potential benefits, the right to withdraw, duration of participation, possibility of alternative treatments, willingness)

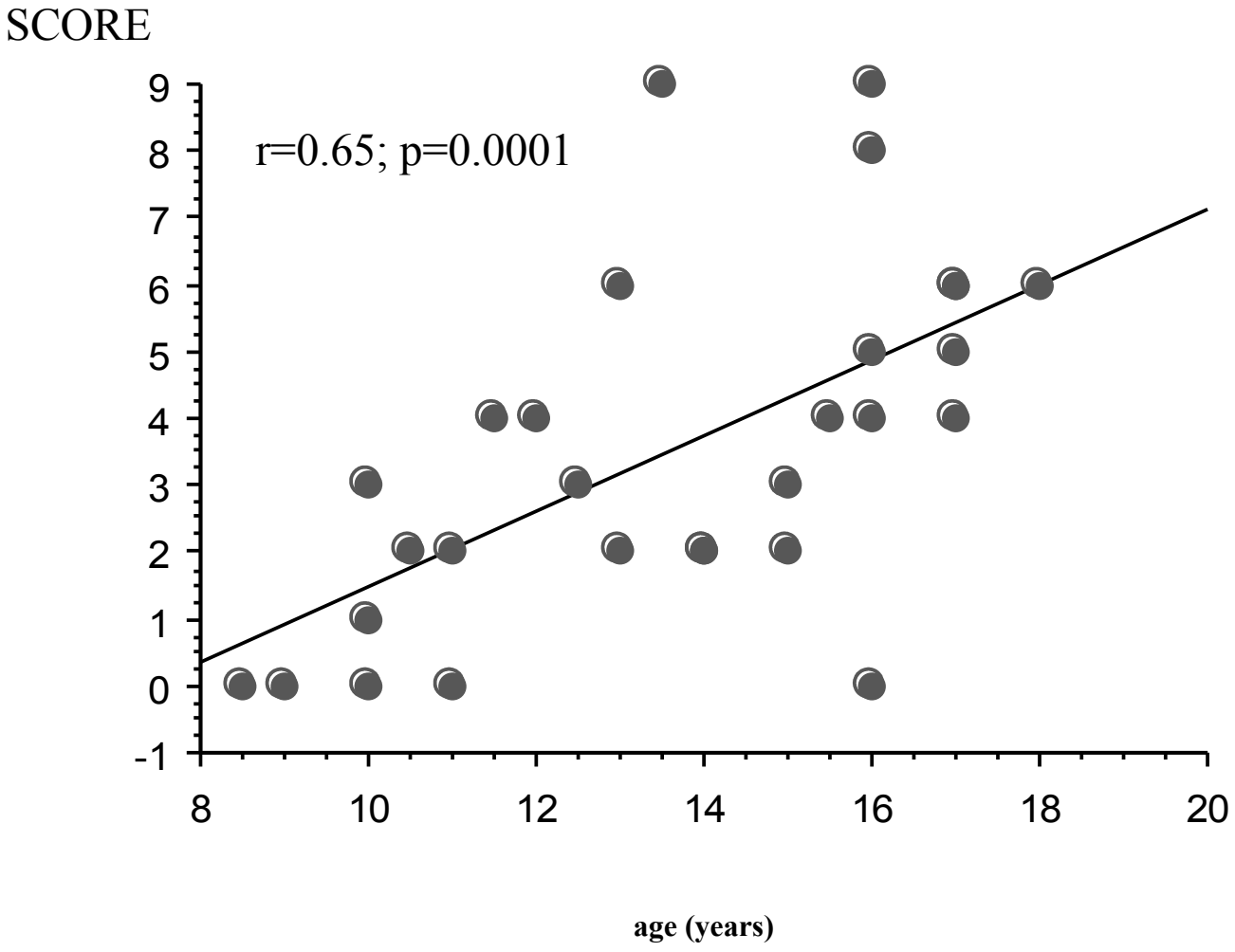

Figure 3: Items of the informed consent understood by children