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PART D

Child participation versus parental authority
NORMS VERSUS PRACTICE: PEDIATRIC ONCOLOGISTS’ ATTITUDES TOWARDS INVOLVING ADOLESCENTS IN DECISION-MAKING CONCERNING RESEARCH PARTICIPATION

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ABSTRACT

Background. Various regulations and guidelines stipulate the importance of involving adolescents in decision-making concerning research participation. Several studies have shown that in the context of pediatric oncology this involvement is difficult to achieve due to emotional stress, the complexity of research protocols and limited time. Still, up to 80% of adolescents with cancer enter onto a trial during their illness. The aim of this study was to determine physicians’ views and attitudes towards enrolling adolescents in research, considering the difficulties surrounding their involvement in decision-making.

Methods. A qualitative multicenter study was performed, using in-depth semi-structured interviews on the informed consent process with 15 pediatric hemato-oncologists.

Results. Four central themes emerged that characterize physicians’ attitudes towards involving adolescents in the decision-making process: (1) physicians regard most adolescents as not capable of participating meaningfully in discussions regarding research; (2) physicians do not always provide adolescents with all information; (3) proxy consent from parents is obtained and is deemed sufficient; (4) physician-investigator integrity: physicians judge research protocols as not being harmful and even in the best interest of the adolescent.

Conclusions. Physicians justify not involving adolescents in research discussions by referring to best interest arguments (adolescents’ incompetence, proxy consent, and investigator integrity), although this is not in line with legal regulations and ethical guidelines.
INTRODUCTION

Informed consent is a major issue in pediatric ethics, especially when it concerns parents’ and children’s consent for research (Committee on Bioethics 1995; National Commission for the Protection of Human Subjects 1979). While adults are assumed to have the requisite capacity to provide an informed consent, children are a protected population and in most circumstances are not afforded the legal right to consent. Often, however, children who have not yet reached the legally established age of consent do have the mental capacity to understand the implications of participating in research. Several studies have assessed children's comprehension of trials (Joffe et al 2006; Mårtenson and Fägerskiöld 2008). They studies suggest that children as young as 9-10 years can understand research-related information, whereas under optimal circumstances, children aged 14 and older can even approach the understanding expected of adults. Still, it is also recognized that age is at best a proxy for developmental capacity, and that experience, maturity and psychological state are important determinant factors.

Numerous country-specific regulations as well as international treaties stipulate the importance of involving minors in decision making concerning research participation (Jaspan et al 2008; Office for Human Research Protections 2009). In addition to the legally required informed consent (permission) from parents, most of these regulations require that assent be obtained from those children who are deemed capable of providing it. Assent is defined as ‘a child’s affirmative agreement to research participation’ (Code of Federal Regulations 1991). Especially in the case of adolescents, serious consideration should be given to their developing capacities for participating in decision making, regardless of legal authority (Committee on Bioethics 1995; Leikin 1993). This mainly implies that meaningful agreement to enroll in a trial should be sought and that any refusal should be respected (Council for International Organizations of Medical Sciences 2002; Council of Europe 2005; Whitney et al 2006). The Dutch Act on Medical Research Involving Human Subjects correspondingly states that the consent of the minor should be sought in addition to the written permission of the parents when the minor is aged 12 or over and is deemed capable of participating meaningfully in decision making. It also states a clear duty to inform all children (whatever age) in a developmentally appropriate manner, while refusal of even young children needs serious consideration.

The intensely emotional nature of pediatric oncology makes it difficult to involve adolescents in decision making (Joffe et al 2006). Complex treatment and research-related decisions are brought up while facing a potentially life-threatening diagnosis, limiting good communication (Dermatis and Lesko 1990; Oleschnowicz et al 2002). Informed participation in decision-making requires the understanding of complex research-relat-
ed concepts such as randomization, voluntariness, and risks. The consent documents explaining these concepts are hard to understand for the layman (Berger et al 2009). Furthermore, most pediatric oncologists are also investigators and consequently discussions regarding diagnosis and treatment often include dialog about participation in research. Due to this integration of research and treatment, it is difficult for adolescents to distinguish between scientific goals and treatment objectives (Chappuy et al 2008; Susman et al 1992; Broome et al 2001). Finally, decisions about research participation need to be made within days or even hours (Stevens and Pletsch 2002). Taken together, the above constraints are likely to limit the degree and quality of discussions concerning trial enrolment. Consequently, assent is difficult to obtain (Oleschnowicz et al 2002). Still, a remarkable percentage of children with cancer—up to 80% of 0- to 14-year-olds and up to 30% of children over 15—enroll in a trial during their illness, as compared to only 1–4% of adult patients (Bleyer 1997; Ferrari and Bleyer 2007).

Little is known about physicians’ attitudes towards involving adolescents in decision making. Few data are available on the presence and degree of participation of children in discussions regarding research (Oleschnowicz et al 2002) and what adolescents think of the assent process (Young et al 2003). No data are available on our research question: what are the views of physicians concerning their ethical and legal obligation to involve children in decision-making and how do they justify the limited extent to which assent is obtained? As we aimed to explore views, experiences, and attitudes, a qualitative interview design was used (Patton 2002; Denzin and Lincoln 2000). The research setting is defined as the situation in which the patient will not receive person-specific standard treatment but will instead be treated according to a clinical research protocol (with or without randomization) in order to obtain generalizable results. Adolescents are defined as minors between the ages of 10 and 18 years.

METHODS

The study sample was drawn from data collected as part of a larger qualitative multicenter project exploring patients’, parents’ and physicians’ experiences of the informed consent process for treatment and research decisions after initial cancer diagnosis or after relapse. The project was approved by the Institutional Review Boards at the study sites. Informed consent was obtained from all participants. The present study is based on the interviews with the subgroup of physicians. One-to-one, in-depth, semi-structured interviews were conducted with the entire medical staff of two pediatric oncology centers in two academic hospitals (n=15). Children and adolescents up to the age of 18 are generally treated in these centers. The interviews were carried out from June to August 2007.
**Interview procedure and analysis**

All physicians were interviewed by the author of this thesis. Initial interview topics (see table 8) were formulated after examination of the relevant literature and a preliminary observational study in the children’s oncological ward of one of the hospitals. In accordance with qualitative research techniques, the interview topics evolved as the interviews progressed through an iterative process to ensure that the questions captured all relevant emerging themes (Britten 1995; Guest *et al.* 2006). The interviews contained general topics and no close ended questions, and lasted between 30 and 60 minutes. Thematic saturation was reached after the 11th interview.

The interviews were recorded and transcribed verbatim. Data analysis was based on the constant comparative method (Strauss and Corbin 1998; Malterud 2001). Two of the authors (MdV and EvL) independently coded the transcripts by identifying and labeling discrete units of texts that referred to one or more concepts relevant to the purpose of the study. Through comparison across transcripts, the open codes were developed into higher order themes to provide a framework for coding subsequent transcripts. An independent researcher coded two transcripts to check for consistency and adequacy of the framework. No inconsistencies were found.

We used qualitative software, Kwalitan 5.0 (Peters 2000), for multiple text management including coding, locating, and retrieving key phrases. Finally, representative quotations were chosen to demonstrate the themes identified. These quotations are included in the text.

**Table 8. Interview Topics**

The in-depth interview topics covered:

- Characteristics of pediatric oncology: integration of research* and treatment, emotional setting
- Possible difficulties in explaining research and treatment goals and risks
- Physician-patient-parent relationship concerning treatment and research decisions
- Adolescent’s participation in decision making
- Ethical and legal obligations to involve adolescents in decision-making
- Parents and patient autonomy
- Physician’s ideas on non-maleficence and beneficence

*When talking about research, we confined ourselves to discussing phase III-trials, in which the overall contribution of a new approach (‘protocol’) was evaluated, often in a large, randomized controlled trial (RCT) setting in which the new approach was compared with the previously evaluated best standard therapy. Most ‘front-line’ pediatric cancer studies are phase III studies.
RESULTS

All 15 physicians who were contacted agreed to participate. The physicians varied in age, sex and working experience (see table 3, page 21). The physicians from center B were younger and had less working experience in pediatric oncology. There were, however, no differences in outcomes according to site.

In line with previous studies, almost all physicians stated that meaningful assent from adolescents, although an ethical (and legal) requirement, is difficult to obtain (12 of the 15 physicians, 80%). Four central themes that characterize the physicians’ attitudes towards involving adolescents in decision-making concerning research were identified. These themes emerged consistently in all interviews.

**Theme 1: physicians regard most adolescents as not capable of meaningful participation in research discussions**

The interviews show that the physicians in our study started from the presumption that adolescents are incapable of participating meaningfully in research discussions, mostly because of the overwhelming situation. All physicians stated that most adolescents are unable to judge correctly what a research setting entails, even after ample discussion.

*In my opinion, these children are not able to judge these things at the time of diagnosis. As soon as I get the idea that they can, I try to involve them in the decision-making. But I think that only concerns the children who really have reached puberty, not the 12- and 13-year olds. Most of them sit and watch their parents.* – Physician B4

Four physicians stated that sometimes they did encounter adolescents who were capable of understanding what research entails, mainly because they were facing a relapse and had previous experience in participating in research.

*It is true that children who suffer relapse, well they are sometimes wiser than you would expect. Not all of course, but some are.* – Physician A5

Children who had almost reached the legally established age of maturity (in the Netherlands: 18 years) were also attributed more capabilities but this was not seen as a general rule. Physicians also encountered older adolescents who were too overwhelmed to participate in research discussions.
**Theme 2: Physicians do not always provide adolescents with all information**

The majority of physicians (11 of the 15 physicians, 73%) will omit information when talking to adolescents because they think they are too vulnerable. Sometimes information is also considered not to be useful for them at that particular moment.

*Most of the times I talk to parents and the child separately, because I’m more honest to parents than to the child about the ins and outs of the research protocol and possible complications. (...) It’s not that I lie about things, but some things you just don’t have to mention to a child. You don’t have to burden a child with things that might not happen at all. But we do have the obligation to articulate these things to parents.* – Physician A3

*If you have to explain randomization to a young adolescent, that is often very difficult. You can explain aspects of the treatment in general. [...] But more difficult issues, like randomization and risks, I discuss with parents separately.* – Physician B3

Adolescents hear about their condition, the proposed treatment and side effects (especially short term side-effects, like vomiting and hair loss), but they get little or no information on certain research issues, such as risks (stated by 9 of 15 physicians), randomization (2 of 15 physicians), alternative treatments (5 of 15 physicians) and extra burdens (2 of 15 physicians). Leaving out information and thus enabling only incomplete participation in decision making was justified with the following arguments: first, proxy consent from parents was obtained (theme 3); and second, physicians judge research protocols as being not harmful and even in the best interest of the child (physician-investigator integrity, theme 4).

**Theme 3: physicians regard proxy consent as a necessity**

All physicians were confident that parents generally want to promote the welfare of their child and that parents understand the research setting. Therefore, proxy consent was seen as sufficient justification for enrolment.

*Some adolescents just don’t understand what they are signing. Then I count on the parents’ wishes. Parents always want what is best for the child.* – Physician A6

**Theme 4: Physician-investigator integrity: research is not harmful**

Thirteen of 15 physicians (87%) felt confident to include a child in a study since their own knowledge of the trial (e.g., its risks and burdens) and the Institutional Review Board (IRB) approval convinced them that the study was not inferior to known treatment options. Their own integrity and IRB control would protect the child.
I’ve seen the development of this trial and that’s why I’m very aware of what we offer the child. It is not something horrifying but something I can support completely. Well, that’s why I don’t have any difficulty that I let the child sign for a trial, although he doesn’t understand the ins and outs of it. – Physician B5

The accuracy that studies need to have these days to be accepted by IRB ruling...; then you can wholeheartedly say that it is not harmful. And that’s why I’m a vigorous advocate of studies and I always try enroll a child. – Physician A4

Some clinicians (3 of 15) said participation in a trial, independent of the arm the patient is in, ameliorates the treatment which could be received outside a trial.

I think that parents should become more familiar with the fact that studies actually provide a qualitatively better treatment. There is better control, there are fixed rules we have to abide by concerning inclusion, exclusion, adjusting chemotherapy because of side-effects, etc. That’s why I’m more inclined to think that participating in a study is an advantage, rather than a disadvantage. – Physician A4

Two physicians were skeptical about the benefits for children.

It’s not true that participation in research is completely harmless. We are fallible. Sometimes experimental arms of research turn out not to work at all. Also, little things can go wrong during the treatment. It’s all human work. – Physician A6

All physicians felt bound to enroll children in the, usually international, clinical trials, because they considered it the state-of-the-art treatment and because the oncological team conformed itself to participate in these trials.

We also explain how things work in the Netherlands, that our hospital works with uniform protocols, that all children get the same treatment in the Netherlands. (...) I have to admit that I explain things [to parents] as if they have no choice. I usually say: your child has leukemia, or whatever form of cancer, and then most of the times I already made copies of the trial protocol outline and I say: well, in the Netherlands all children with this disease are treated this way. – Physician B1
DISCUSSION

In pediatric oncology, treatment is often combined with research. The intertwinement between research methodology and clinical care has led to much progress in therapeutic options, but it makes the informed consent procedure difficult to perform. The physicians in our study confirmed that they often do not fully involve adolescents in decision-making concerning research participation. Assent by the adolescent is acknowledged as ethically and legally necessary but is said to be difficult to obtain.

The four themes that characterize the physicians’ attitudes towards involving adolescents in research discussions can be summarized as follows: Adolescents are not capable of meaningful participation in these discussions (theme 1) and are not fully involved in decision-making (theme 2). This is, however, not a problem, because proxy consent (theme 3) and investigator’s integrity (theme 4) safeguard the adolescent’s best interest in a trial. Not involving adolescents in research discussions is justified by physicians with the use of best interest arguments (adolescents’ incompetence, proxy consent, and investigator integrity). Discussion should focus on the appropriateness of these best interest considerations in a research setting.

Best interest and research participation

Almost all pediatric oncologists in our study sincerely believed that enrolling children in clinical trials was in their best interest and constituted state-of-the-art treatment. These observations support Joffe et al’s findings about enrolment of children in trials and best interest considerations (Joffe et al 2002).

At first sight, it seems rather safe to rely on a best interest standard in research decisions since the same standard is used in treatment decisions. In a research context, however, proxy consent and the best interest standard are not so easily applied. First, the function of proxy consent can be troublesome: literature shows that parents also have difficulties in understanding research related topics (Stevens and Pletsch 2002; Kodish et al 2004; Wiley et al 1999). What is more, there is evidence that there is a potential for disagreement between adolescents and parents on research participation (Young et al 2003). One study even reports a consistent 40% discordance in views between adolescents and parents across a variety of asthma research protocols (Brody et al 2005). It seems that the physicians we interviewed are unaware of the basic lack of understanding of research-related concepts in parents and the potential for disagreement between adolescents and parents. At least it does not change the importance the physicians attach to proxy consent. Based on the literature however, it can be argued that parents may not be equipped to make decisions about research participation on behalf of their children.
Secondly, the contexts of treatment and research are fundamentally different and require different ethical approaches (National Commission for the Protection of Human Subjects 1979; Miller and Brody 2003; Spinetta et al 2003). In the treatment relationship, the best interest of the individual child is prevailing in the selection of the best available treatment. Any new knowledge generated is incidental to the overriding goal of providing therapy. The concept of presumed or implicit consent is often used in the therapeutic setting. Pediatricians routinely carry out medically indicated procedures on children without obtaining assent, or even despite a child’s vigorous objections. This is acceptable because it is the interest of the child which is the sole motivation prompting the intervention (Lee et al 2006). In the context of research, however, the researcher seeks to advance knowledge to improve the care of future children as well as to serve other interests, like building an academic profile. Therapeutic benefits to the individual are, from a methodological perspective, secondary to the overriding goal of obtaining robust data and new knowledge (Miller and Brody 2003). The goals of research often require that children undergo non-therapeutic procedures, such as additional blood samples, spinal taps and (PET) scans. These procedures may cause considerable pain, discomfort, inconvenience, or even harm (Miller and Brody 2003). Therefore, the research setting leaves no room for presumed consent. Subjects should voluntarily enter the research setting, with adequate information and only after explicit consent, because the best interest standard is not the only demanding principle (National Commission for the Protection of Human Subjects 1979).

Sometimes it is argued that an RCT preserves the basic treatment related duty to act in the best interest of the child through clinical equipoise, the uncertainty principle. After all, no subject is randomized to a treatment known to be inferior to the present standard. For example, Kumar et al (2005) found that new treatments in childhood cancer tested in randomized controlled trials are, on average, as likely to be inferior as they are to be superior to standard treatments, confirming that the uncertainty principle has been operating. However, the uncertainty principle also means that it is never known in advance what the actual risks and benefits will be: only after the completion of a study one genuinely knows which trial arm showed the best results and whether or not participants were exposed to extra risks and burdens. Most pediatric oncology trials have Data and Safety Monitoring Plans (DSMP) and stopping rules for the very purpose of dealing with unexpected risks and outcomes.

The physicians in our study argued that trial participation is beneficial as compared to non-participation because of a strict adherence to well-defined protocols. Various authors have stated that the use of treatment protocols improves the end result of treatment (Stiller and Eatock 1999; Karjalainen and Palva 1989; Stiller 1994). This could be
the result of the explicit description of the treatment phases and their follow up. Other authors, however, show that there are insufficient data to conclude that such a trial effect exists (Vist et al 2008; Peppercorn et al 2004). Until such data are available, patients with cancer should be encouraged to enrol in clinical trials on the basis of trials’ unquestioned role in improving treatment for future patients.

In conclusion, recognition of the fundamental conceptual difference between the care orientation and the research orientation is crucial in deciding to obtain explicit assent of adolescents. One cannot justify wavering assent from an adolescent for research elements in a protocol by pointing to the best interest standard, as the physicians in our study did.

**Can adolescents decide for themselves?**
The other reason given by the clinicians for not obtaining assent is that adolescents would not be capable of participating meaningfully in research discussions and that therefore obtaining proxy consent suffices. However, several studies have shown that children aged 14 and older can approach the level of understanding of adults (Joffe et al 2006; Mårtenson and Fägerskiöld 2008). Some studies even conclude that relatively young children (as young as 7 years) can participate meaningfully in the consent process (Committee on Drugs 1995). One study indicates that emotional factors are more frequently related to understanding the implications of research participation than are age or cognitive development (Dorn et al 1995). This suggests that providing a medical environment that decreases anxiety and increases a sense of control may enhance adolescents’ understanding of the research process, however difficult this may be to achieve in the situation of a child with newly diagnosed disease or relapse. The ability to understand research issues may also relate to experience rather than to age, as even young children appear to understand complex issues (British Royal College of Pediatrics 2000). The physicians in our study confirmed these latter findings. Some mentioned that they do encounter children who are wiser than expected and that their approach then is different, involving these children more in the decision-making process. From these data, we can at least conclude that adolescents as a class should not be regarded as incapable, but that an assessment is needed in each individual case. We must aim at avoiding two kinds of mistakes: imposing complex research decisions on adolescents who are unwilling or unable to make them, and excluding capable adolescents who desire to participate in decision making (Joffe et al 2006). Therefore, a case-by-case (psychological) assessment prior to concluding the consent process is necessary in order to evaluate the decision-making capacity of the adolescent (Abrams et al 2007). Thus, justice may be done to the ethical ideal of respect for the developing autonomy of children in making decisions, as
Chapter 6

stipulated in several international regulations and guidelines [Code of Federal Regulations 1991; Directive 2001/20/EC 2001; Spinetta et al 2003). Unless they have a very pertinent reason to do so, physicians cannot put their judgment about the child’s best interest in place of the child’s consent to participate. The opinion of the adolescent should be actively sought, which will sometimes mean that the views of parents will have to be overridden by oncologists. We would suggest that in the case of an adolescent with the capacity to understand the implications of research participation, both the adolescent and the parents need to consent to research participation. Especially an adolescent’s refusal needs serious consideration; in our view conducting research is not acceptable if this means overruling an adolescent’s refusal, even if parents did consent to it.

It is extremely difficult to explain complex research concepts to lay persons in a situation of acute, serious medical illness as well as emotional strain. Well-crafted information materials (booklets, visual aids) could aid investigators in explaining to potential child research participants and their parents what these concepts mean, and which elements of their treatment are research procedures (for example additional blood samples or spinal taps) (Ungar et al 2006).