Editor-in-Chief's Note

Informed Consent and Assent in Pediatric Oncology Trials

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Although losing a child of any age is unimaginably painful for any parent, losing a young child to cancer is devastating. Desperation in such cases may lead parents to make irrational choices in an effort to save the child. When the treating clinicians know they have exhausted all conventional therapeutic approaches, enrolling the child in a clinical trial is often the next consideration. What do parents need to know to give informed consent for the participation of a child in treatment research? Beyond presenting the basic facts about a particular cancer, any investigational study will involve questions of risk vs benefit that, by definition, are initially unanswerable. This is particularly true for Phase 1 trials for which there may be minimal evidence to support any expectation of a positive outcome. Can parents, in their panic and hopelessness, make a rational decision? Can the desperation of parents or the poor prognosis for a child pressure a clinician to enroll a child who does not meet all entry criteria? When should the affected child be asked to give her or his assent to participation? How can the facts be explained to children, and how should this information be conveyed to children and by whom? I have asked my wife, Cynthia, to join me in offering some perspectives that have emerged from our discussions of this vexing topic. Cynthia, a retired educator, has served for 20 years as a community member of our local hospital's institutional review board.

An informed parent must thoroughly understand what it means to have a child take part in the proposed clinical trial. Can a parent be fully informed about the benefits and risks of the experimental agent (or other research strategy) being offered for their child? If not fully informed, then how much does the parent need to know? Do the parents understand key features of the study design, such as the potential for their child to receive suboptimal doses in Phase 1 studies or control treatment in randomized clinical trials? Are their expectations consistent with the study design? Do the parents really feel that they have a choice and that participation is voluntary? Can they discuss what circumstances would lead them to withdraw their child from the research protocol?

Investigators must do their best in the consenting process to provide what is known and what is not known to the parent(s). They need to describe what will be expected of the parent and what the child will be going through —to the extent that this information is known. Consenting should be a process that includes unhurried interactive discussion. For that reason, *permission* may be a fuller, more accurate term of agency than *consent*. We propose that this term becomes the standard in discussions with parents and children. Parents may request the participation of an advocate they choose; particularly when not conversant in English, they will need a qualified medical translator to assist in understanding the facts and expectations. They may need similar support and assistance in non–English-speaking countries. A signed document that concludes the consenting process serves as a

record of the discussion and details procedures for possible withdrawal. The parent(s) should be given a copy to take home.

Additional background information is warranted before we delve into the complexities of informed consent and assent for cancer studies that involve children and youth. Although unintentional injuries are the leading cause of death among youth and children, solid tumors in the brain and elsewhere and hematologic cancers are the next most common causes. Deaths from hematologic cancers are decreasing, most likely because they involve clonal proliferation for which specific and targeted treatments are now more successful.[1,2] In older youth, gonadal cancers, melanomas, and other cancers begin to emerge, although they are less likely to be lethal.[2] From the mid-1970s to the period between 2006 and 2012, relative survival rates for all forms of cancer in children and adolescents increased from 58% to 83% and 68% to 84%, respectively.[2] Perhaps because of the success in treating hematologic cancers in children, a larger proportion of children compared with adults are enrolled in clinical trials of anticancer agents.[3]

Although there is every reason for optimism in the battle against cancer in young people, the picture is not entirely rosy. Greater than 80% of children treated with currently available methods can expect to survive into adulthood.[4] Often overlooked, however, is the association of long-term survival with unwanted health-related sequelae that appear well after cessation of treatment. Sometimes referred to as *late effects,* these sequelae can include chronic health problems in more than 50% of patients; between 20% and 80% will experience severe or life-threatening complications at some time during adulthood.[4]

The beginning point in any discussion of informed consent or assent is age, with different considerations for consent by parents and assent by youth and children. Let us begin with an extreme example—a 17-year-old single mother whose 2½-year-old child has a Wilms tumor,[5] a solid tumor in a kidney that most often occurs before the age of 6 years. Also known as a nephroblastoma, it accounts for approximately 20% of the cancers that affect this youngest age group. In our hypothetical case, surgery has been performed, and follow-up chemotherapy is under consideration. Staging and histologic findings are consistent with a suboptimal prognosis. A nearby hospital is a site for a clinical trial of a new agent as an alternative to the customary drugs dactinomycin and vincristine. A rarer example could be a retinoblastoma, a malignant tumor in the eye, in a 2-year-old whose mother is 16 years old.

These hypothetical cases raise a number of questions: How old must a mother or father be to give consent for their child to participate in a research project? At what age and in what form should a preschool child be provided with information about a trial? What is the best way to ensure that young parents understand what is likely to happen and what is required of their child? Are the regulations clear and explicit for cases that involve minor parents? Although the legal age of majority, and thus for consent to enroll in a clinical trial, is earlier in other countries—16 years in some European nations (eg, Austria)—under US federal law, an age of 18 years is the rule. However, some American 16- and 17-year-olds may attain mature or emancipated minor status by way of marriage, court order, or a financially independent living arrangement. Even in a state where minors are not deemed emancipated, they may still have the right to consent to basic medical care for their children. That said, there is no consensus regarding a minor's right to enroll her or his child in investigational research, an ethically more complex undertaking than the simpler right to consent to the child's medical treatment.[6,7] Thus, when faced with a decision whether to enter their very sick children in a research protocol, the mothers in our hypothetical cases are likely to be unprepared to handle these challenges alone. If the father is available and involved, both parents are required to give consent.

Respect for persons, a fundamental prerequisite of ethical research, aims to ensure that consent is voluntary and not affected by adverse situational factors or inappropriately interested family members or professionals. Even with an acceptable seventh-grade reading level and school-tested comprehension, the adolescent parents of a child newly diagnosed with cancer, assuming the parents have no experience with health literacy, will feel particularly vulnerable during the consent process.[8] They are likely to need extra help, such as tutorial with a nurse advocate, to overcome the disadvantage of health illiteracy.[9] They are likely to have trouble understanding let alone accepting that research may yield knowledge but cannot promise direct benefit to their child. However, an understanding of the risks in taking part, and in not taking part, is crucial to their decision-making autonomy. The