Editor-in-Chief's Note

Informed Consent and Assent in Pediatric Oncology Trials

Richard I. Shader, MD

Cynthia H. Livingston, ALM, MAT

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

presence of an independent advocate or a supportive family member is usually advisable.[10] Best practices for obtaining consent must always be followed.

For our hypothetical cases, the affected toddlers are too young to give assent. Meaningful understanding of the concept of illness or the irreversibility of death is typically established at approximately 4 or 5 years of age. Efforts to help the young child understand the situation are best accomplished through play and the use of drawings or other pictorial material. Older children typically benefit from discussion that include their parent(s) and from developmentally geared media presentations.

Early childhood cancers continue to occur despite significant advances in detection and treatment. We advocate refinements in applicable regulations that govern the medical-pediatric experience of teenage mothers and fathers of children with cancer so that attention will be given to the particular needs of these young parents and their children. Although the rate of teenage motherhood is decreasing in the United States and United Kingdom, there remains a critical need for regulatory guidance for these young parents.[11,12] This issue is especially a concern in some jurisdictions where access to contraception is unavailable or may become restricted.

In the late 1990s, we conducted a multisite population pharmacokinetics study of methylphenidate in 273 young volunteers 5 to 18 years of age.[13] Written assent was obtained in addition to parental consent for all these children. As the study was proceeding, we wondered how our study participants felt about their participation in this minimally invasive project. Shortly after the study was over, we contacted most of those who participated. Assessed in retrospect, most children (1) considered their participation to have been completely voluntary, (2) remembered that the information given to them about the study was accurate, and (3) were positive about having been in the study.[14] At the time of our study, there was a dearth of literature that informed investigators about the participation of children and youth in clinical trials. Since that time, more studies and guidelines have become available.

Unfortunately, there are still gaps and ambiguities that need to be clarified. Several studies[15–23] provide additional useful information, insights, and recommendations. As far as we could discover, however, there is no literature on how clinicians decide to refer their cases for pediatric oncology trials or for other trials of investigational drugs. Whether any referral bias affects the results of Phase 1 trials and their subsequent interpretation remains an unanswered question.

Our special topical update this month is entitled Pediatric Oncology Drug Development: Meeting Unmet Needs and Regulatory Demands. The selected articles were assembled by our Topic Editor for Drugs and Biologics development, Dr Kenneth I. Kaitin.[24–27] Because there are regulatory differences in many countries about involvement in pediatric oncology trials, as well as differences in attitudes and information available to parents and their affected children, we invite our readers to submit for consideration letters to the editor that elucidate standards and practices in countries across the world wherever pediatric oncology trials are conducted.

Richard I. Shader, MD
Editor-in-Chief
and Cynthia H. Livingston, ALM, MAT

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66:7–30.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67:7–30.
3. Berg SL. Ethical challenges in cancer research in children. *Oncologist*. 2007;12:1336–1346.
4. National Cancer Institute. Late Effects of Treatment for Childhood Cancer (PDQ®)–Health Professional Version. https://www.cancer.gov/types/childhood-cancers/late-effects-hp-pdq. Accessed January 11, 2017.
5. American Cancer Society. Wilms tumor. http://www.cancer.org/acs/groups/cid/documents/webcontent/003149-pdf.pdf. Accessed January 11, 2017.
6. Institute of Medicine (US) Committee on Clinical Research Involving Children. State regulation of medical research with children and adolescents: an overview and analysis. In: Field MJ, Behrman RE, editors. *Ethical Conduct of Clinical Research Involving Children*. Washington, DC: National Academies Press; 2004.

7. Miller VA, Nelson RM. Factors related to voluntary parental decision-making in pediatric oncology. *Pediatrics*. 2012;129:903–909.
8. Nelson LR, Stuplansky NW, Ott MA. The influence of age, health literacy, and affluence on adolescents' capacity to consent to research. *J Emp Res Human Res Ethics*. 2016;11:115–121.
9. Foe G, Larson EL. Reading level and comprehension of research consent forms: an integrative review. *J Emp Res Human Res Ethics*. 2016;11:31–46.
10. Institute of Medicine (US) Committee on Clinical Research Involving Children. Understanding and agreeing to children's participation in clinical research. In: Field MJ, Behrman RE, editors. *Ethical Conduct of Clinical Research Involving Children*. Washington, DC: National Academies Press; 2004:1–43.
11. Romero L, Pazol K, Warner L, et al. Reduced disparities in birth rates among teens aged 15-19 years – United States, 2006-2007 and 2013-2014. *MMWR Morb Mortal Wkly Rep*. 2016;65:409–414.
12. Wellings K, Palmer MJ, Geary RS, et al. Changes in conceptions in women younger than 18 years and the circumstances of young mothers in England in 2000-12: an observational study. *Lancet*. 2016;388:586–595.
13. Shader RI, Harmatz JS, Oesterheld JR, et al. Population pharmacokinetics of methylphenidate in children with attention-deficit hyperactivity disorder. *J Clin Pharmacol*. 1999;39:775–785.
14. Fogas BS, Oesterheld JR, Shader RI. A retrospective study of children's perceptions of participation as clinical research subjects in a minimal risk study. *J Dev Behav Pediatr*. 2001;22:211–216.
15. Children's Oncology Group. Informed consent. https://childrensoncologygroup.org/index.php/informed-consent-311. Accessed January 11, 2017.
16. National Cancer Institute. Children's assent. https://www.cancer.gov/about-cancer/treatment/clinical-trials/patient-safety/childrens-assent. Accessed January 11, 2017.
17. Kupst MJ, Patenaude AF, Walco GA, et al. Clinical trials in pediatric cancer: parental perspectives on informed consent. *J Pediatr Hematol Oncol*. 2003;25:787–790.
18. Simon C, Zyzanski SJ, Eder M, et al. Groups potentially at risk for making poorly informed decisions about entry into clinical trials for childhood cancer. *J Clin Oncol*. 2003;21:2173–2178.
19. Simon CM, Siminoff LA, Kodish ED, et al. Comparison of the informed consent process for randomized clinical trials in pediatric and adult oncology. *J Clin Oncol*. 2004;22:2708–2717.
20. Roth-Cline M, Nelson RM. Parental permission and child assent in research on children. *J Biol Med*. 2013;86:291–301.
21. Miller VA, Baker JN, Leek AC, et al. Patient involvement in informed consent for pediatric phase I cancer research. *J Pediatr Hematol Oncol*. 2014;36:635–640.
22. Informed Consent. http://ec.europa.eu/research/participants/data/ref/fp7/89807/informed-consent_en.pdf. Accessed January 11, 2017.
23. Children's Cancer and Leukaemia Group. Children and Young People With Cancer: A Parent's Guide. http://www.macmillan.org.uk/documents/cancerinfo/childrenscancer/childrenandyoungpeoplewithcancerparentsguide_cclg.pdf. Accessed January 11, 2017.
24. Kaitin KI. Drug development for pediatric oncology indications: regulatory, scientific, and economic challenges. *Clin Ther*. 2017;39:236–237.
25. Milne CP. More efficient compliance with EMA and FDA regulations for pediatric oncology drug development: problems and solutions. *Clin Ther*. 2017;39:238–245.
26. Rose K. New drugs for rare diseases in children. *Clin Ther*. 2017;39:246–252.
27. Rose K, Walson PD. Do the European Medicines Agency (EMA) decisions hurt pediatric melanoma patients? *Clin Ther*. 2017;39:253–265.

http://dx.doi.org/10.1016/j.clinthera.2017.01.024