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### **Re: Views of American Oncologists About the Purposes of Clinical Trials**

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In a recent article in the *Journal*, Joffe and Weeks (1) reported that most pediatric oncologists offered their patients the opportunity to enroll in trials to ensure that their patients received “state-of-the-art” therapy and that nearly 40% of responding pediatricians “reported that trials exist primarily to ensure state-of-the-art therapy for the participants themselves.” In an accompanying editorial, Miller (2) worried that a substantial proportion of pediatric oncologists might misconceive the purpose of clinical trials, thereby creating a “therapeutic misconception” for the children and families who agree to trial participation, as well as for the oncology teams treating those children.

Pediatric cancer specialists in North America have cooperatively designed and conducted sequential, randomized phase III clinical trials for more than four decades to use evidence-based information to refine the treatment of children with cancer. The state-of-the-art treatment for a child with cancer derives from the best therapy identified in prior clinical trials, and this best-available treatment serves as the standard arm of subsequent phase III clinical trials. Thus, the standard arms of clinical research protocols serve as *de facto* practice guidelines, and newly diagnosed children can receive this state-of-the-art standard therapy whether or not they enroll in a clinical research trial.

The national pediatric phase III cancer therapy studies are reviewed by multiple panels of childhood cancer experts to ensure that all treatment arms comply with current best-available therapy. Once a trial is initiated, data monitoring committees are charged with stopping the study if sufficient evidence develops to demonstrate that treatment outcome or toxicity no longer conform to best-available therapy. By investigating incremental modifications of best-available therapy in sequential phase III studies, pediatric oncology specialists have learned to employ radiotherapy, surgery, and a limited number of common chemotherapy agents in a risk-based manner, thereby generating steady improvements in patient outcome. For example, 5-year survival for children with acute lymphoblastic leukemia, which was less than 5% in the early 1960s, increased to approximately 50% in the mid-1970s and to 85% by the mid-1990s.

The academic environment in which most pediatric oncologists practice allows physician-investigators to pursue clinical research as a means to improve treatments. However, this pursuit sets up a potential conflict between the practitioner’s dual roles as clinician and investigator. In recognition of this potential conflict, the Children’s Oncology Group has studied the informed-consent process (3,4) and is working to clarify and improve both the decision-making process that families encounter and the information provided by the pediatric oncology team. Efforts to discriminate between the experimental and the standard treatment components of a protocol’s diagnostic and therapy requirements have been augmented. The goal of these efforts is to help families and their physicians better understand how research questions affect potential study participants and better determine whether study enrollment is the most appropriate choice for a particular child.

Pediatric cancer specialists are committed to clinical research because they understand that well-designed clinical trials with appropriate safeguards are the best path to identifying and delivering more effective therapies, while at the same time providing treatment that is consistent with current best-available therapy. Society, and especially children diagnosed with cancer, continues to be well served by the dedicated clinical care and clinical research efforts of the

health care professionals specializing in pediatric oncology.

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## NOTES

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## RESPONSE

We welcome the thoughtful correspondence by Anderson et al. about our recent paper on American oncologists' views of clinical trials (1), and we second their comments. These investigators correctly highlight the exemplary work of the pediatric oncology community over the past few decades in improving outcomes for children with cancer. The clinical trials program in pediatric oncology, which has served as the foundation for these advances, constitutes an international model for sustained and systematic improvement in the state of the clinical art (2).

We particularly appreciate the authors' characterization of the standard arm of a randomized phase III trial as state-of-the-art treatment that is available to patients whether or not they en-

roll in a trial. This characterization, which implies that the experimental arm represents a (generally reasonable) deviation from the standard of care, brings much-needed clarity to our thinking about clinical research.

The data we reported suggest that the ethical challenges inherent in all clinical research may be particularly acute in pediatric oncology, perhaps because of the unparalleled integration of trials into the routine care of pediatric cancer patients. To its credit, the pediatric oncology community has engaged in valuable dialogue and research about the complexities of conducting clinical trials among children with cancer (3-6). We join Anderson et al. in underscoring the fundamentally ethical nature of this research enterprise and salute the dedication of all who contribute to this important effort.

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## NOTES

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