Ethical Considerations for Oncology Clinical Research
In clinical research, we recognize that all trials involve a certain level of complexity. But in no specialty is this truer than in oncology. Oncology research has opened new and promising avenues of investigation thanks to significant advances in the areas of personalized medicine, immunotherapy and human gene transfer research.

To accommodate these scientific advances, newer, more complex forms of clinical trial design have emerged. Moving away from the traditional phased model of study design, sponsors are exploring concepts like the basket trial, efficacy assessments in translational and early-phase studies, adaptive designs, and other novel methods intended to speed the drug development process.

Medical innovation has always brought with it associated ethical issues. The new therapeutic technologies – and advances in the field of oncology – create new ethical considerations. And sometimes, they also bring new considerations to long-standing ethical discussions.
There are few areas of medicine in which clinical research has become as intertwined and integrated with clinical care as in oncology.

In fact, many cancer centers promote their medical services by advertising the number of clinical trials they conduct or that patients will have “access to the newest investigational treatments”, even though both the efficacy and safety of those treatments are still being studied. Therapeutic misconception, defined as the clinical trial participant being unable to fully understand that they are participating in an experimental research study rather than receiving regular medical care, can be a significant problem in cancer research.

The ethical concept of equipoise in clinical trials ensures that participants would not be enrolled in a study in which it is known that one regimen they might receive is inferior to the other; the corollary is there is not enough evidence yet to know which arm may be superior. Study participants may not understand that the regimen they are undergoing is still of unknown risk and benefit rather

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than what the oncologist has selected as the best available care for their specific circumstance. Oncology patients can also forget that the investigational drug – although newer – may not turn out to be better than the available standard of care. In some cases, it may actually be worse in efficacy, safety, or both. When participants don’t understand that their care is experimental rather than standard, they can also misunderstand their ability to withdraw from a study (and perhaps receive other available therapies).

While research participants can, and should, be optimistic about their chances for response to investigational treatments, they must still understand that the treatments are experimental. Several studies have shown that participants overestimate the possibility that they will have a significant tumor response in early phase studies designed only to find a safe dose of study drug, even when they are provided with accurate information about their chance of response during the consent process. It can be difficult to determine whether this discrepancy is the result of optimism or lack of understanding regarding the very low possibility of therapeutic benefit, which may then be inaccurately assessed against the potential risks of study participation.
Contributing to ethical challenges are the complications of conducting research in patients who may not have other good therapeutic options – or who may have no other therapeutic options at all.

While this is not a situation unique to oncology, it does occur frequently in this field. When both the health care team and the patient desperately hope to find something to reverse or delay the course of the disease, it can be very difficult to convey or to comprehend the actual risks and benefits of study participation, respectively.

The need to conduct well-controlled clinical trials adds complications as well. When there are no good treatment options, patients and families are reluctant to risk enrollment in a control (which may be supportive care, if that is the standard care) or placebo arm. They fear both the progression of the disease during the course of the study and the potential loss of an opportunity to try what may be a new effective therapy. However, without appropriate control groups, improvement in the symptoms or disease endpoints is very hard to determine objectively, and that evidence is needed to support the continued development and approval of a new therapy. Knowing that the investigational drug may or may not be the treatment everyone hopes for – and ensuring that an accurate assessment of the risks and benefits of therapy is conducted while allowing for optimism – is a continual challenge in the informed consent process.
The last several years have brought tremendous advances in the therapeutic technology of new cancer treatments. Many of these products look very promising in early clinical development and more products are now moving into the later stages of development. But with these new and exciting products comes new scientific and ethical considerations that emerge, particularly in the assessment of the potential risks and benefits (and ability to minimize those risks). This is an essential part of the protocol assessment for Institutional Review Boards (IRBs) and researchers.

For example, gene transfer products are moving into phase 3 studies in greater numbers. These products use recombinant or synthetic DNA, and some include the use of viral vectors for the delivery of the genetic sequence. While many of the safety issues identified in early gene therapy studies have been addressed, there are still unknown questions about the real or potential risks of occurrences like insertional oncogenesis, germ-line transmission, and viral shedding. Immunotherapies, which act by stimulating the immune system to fight disease, including cancer, often work in a dose-independent manner (so that the traditional dose-identifying early stage study is less important), and may be

Continued on next page...
Assessing Risk and Benefit

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so directed toward the human immune system that toxicity studies in animals are inaccurate predictors of human safety risks.

Certainly the risks of new therapies are always unknown, and the clinical risk profile is developed as drugs progress through clinical development. But unknown mechanistic risks add additional considerations to that calculation. It is essential to partner with IRBs – and in the case of gene transfer products, Institutional Biosafety Committees as well – that have a good understanding of the science behind the new therapies, so that they are well-prepared to assess the ethical issues of the protocol.