VIEWPOINT

EVOLVING ISSUES IN ONCOLOGY

Modernizing Clinical Trials for Patients With Cancer

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Clinical trials involve evaluating and validating new therapies in humans and represent the fundamental means of making progress in cancer care. The oncology community has made significant improvements in treating most cancers and, in some cases, has developed cures, such as for testicular cancer, Hodgkin disease, and acute lymphocytic lymphoma. In an even larger number of cancers, researchers and clinicians have succeeded in making cancer a chronic disease that people die *with* rather than *of*. Each of these therapeutic discoveries represents the results of clinical trials.

Many of these advances were made possible in large part through the Clinical Trials Program at the National Cancer Institute (NCI). This program began in 1955,[1] and since then has changed substantially in its approach to the design, coordination, and implementation of clinical trials. The past 10 years, in particular, have seen a transformational reworking of the NCI's clinical trials infrastructure.[2] The NCI National Clinical Trials Network (NCTN) now includes more than 3000 study sites across the United States and Canada and each year enrolls more than 20 000 children and adults with all types of cancer in clinical trials.[3]

The NCTN portfolio includes studies across the cancer research continuum, from first-in-human trials of new agents, to evaluations of new diagnostic and therapeutic techniques, to trials evaluating cancer prevention and symptom management. The infrastructure provides a broad range of support services, including centralized institutional review boards; clinical trials monitoring, data acquisition, and management systems; tissue banks; and quality-control centers for imaging and radiation therapy.

Rethinking Clinical Trials

Cancer clinical trials have important and increasing challenges. In response, NCI, as the leading funder of academic cancer clinical trials, has made modernizing clinical trials a key area of focus.

In addition to a strong recommitment to using the best basic science to drive trials and providing infrastructure for the training of the next generation of cancer clinical trialists through support for early-stage investigators, NCI is using specific strategies to overcome barriers impeding the execution of clinical trials.

Reduce Financial Pressures of Clinical Trials

The average per-patient cost of conducting a clinical trial has increased sharply over the last 2 decades, driving an escalation of the total costs of drug discovery and development. Once a drug is approved, the high costs of trials are then passed on to patients in the form of higher drug prices.

The NCI is therefore focused on "right-sizing" trials to answer essential questions about the efficacy of new treatments with fewer patients. For example, in some trials of highly active agents, it may be possible to forgo traditional control group interventions in favor of well-annotated "synthetic" controls created with data from previous trials. The NCI is also exploring the use of novel end points that reflect the mechanism of action of the drug under study through "pragmatic trials" that are conducted in clinical practice settings and through augmented annotation and aggregation of new and existing trials data to answer relevant clinical questions without additional enrollment.

Conduct Trials That Complement Those of Industry

The emergence of industry as the majority funder of cancer clinical trials has led to redundancies in the portfolio of novel agents in development, with the unintended consequence of crowding out some meritorious ideas for therapy in the search for more commercially lucrative ones. Consequently, the NCI has been positioning its clinical trials portfolio to complement, rather than compete with, efforts from industry.

National Cancer Institute–supported trials are prioritized scientifically by leaders in oncology research. Trials sponsored by the NCI that complement those supported by industry, can, for example, focus on low-prevalence cancers for which there is limited commercial incentive to sponsor clinical investigations, such as pediatric cancers, uncommon cancers, rare subtypes of more common tumors, and special patient populations (eg, patients with HIV or >75 years). The NCI-funded Dual Anti-CTLA-4 & Anti-PD-1 blockade in Rare Tumors (DART) (NCT02834013) national trial, for example, is the first immunotherapy trial focused on rare cancers.

The NCI has supported clinical trials focused on deescalation of therapeutic intensity, which is an important topic for patients but typically of less interest to industry. For example, the Trial Assigning Individualized Options for Treatment (Rx) (TAILORx)[4] and the International Duration Evaluation of Adjuvant Therapy (IDEA)[5] trials showed that certain patients with breast and colorectal cancer, respectively, may be safely treated with less chemotherapy than previously recommended. In addition, the NCI prioritizes complex multiagent and multimodality (eg, radiation therapy, surgery, and chemotherapy) trials, especially those involving established (off-patent) agents, such as taxanes and corticosteroids. Moreover, the NCI

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supports a substantial portfolio of supportive care, cancer prevention, and screening studies that are not extensively supported by commercial sponsors, including studies of breast imaging modalities (eg, TMIST [NCT03233191]).

Facilitate Access to Investigational Agents

The NCI has created partnerships with industry, pioneering a shared intellectual property framework and an efficient mechanism for accelerating clinical trial proposal review. The NCI Formulary facilitates arrangements between pharmaceutical companies and investigators at NCI-designated cancer centers to expedite access to promising novel combinations of anticancer investigational agents sourced from multiple companies for use in preclinical and clinical studies.

Base Trials on Molecular Alterations

A key challenge and a sign of scientific progress involves the recognition that individual cancers, even of the same histological subtype, are molecularly heterogenous. These diseases are generally not well served by large, one-size-fits-all trials. Instead, the NCI has developed novel types of trials that enroll participants based on their molecular alterations, rather than their disease type. This approach limits these trials to patients who are most likely to benefit from a specific treatment and reduces the size of the trials to the smallest number of patients needed to demonstrate therapeutic efficacy.[6] These trial designs often use "Master Protocols" to evaluate multiple classes of therapeutic agents simultaneously.[7] Examples include NCI Molecular Analysis for Therapy Choice (NCI-MATCH) (NCT02465060), which is evaluating a pharmacopoeia of molecularly targeted agents based on the presence of specific tumor mutations in a disease-agnostic fashion, Lung Cancer Master Protocol (Lung-MAP) (NCT02154490), and NCI-COG Pediatric MATCH.

Improve Accrual Rates

An ongoing challenge is low accrual to clinical trials, especially among underserved populations. Only a small fraction of eligible adult patients with cancer are able to participate in clinical trials. Clinical research has traditionally been conducted at academic medical centers, primarily cancer centers. But the populations that cancer centers reach are less diverse than the population overall. Because most patients receive cancer care in community settings, the NCI established the NCI Community Oncology Research Program (NCORP)[8] to bring cancer prevention and treatment trials to minority and underserved patient populations in a variety of health care delivery settings in their own communities. NCORP gives patients access to trials in which they might not otherwise be able to participate and not only increases the generalizability of study findings but also illuminates potential disparities in outcomes. The NCI-MATCH trial, for example, is available at 1100 sites across the country through NCTN and NCORP, leading to enrollment that better reflects the overall patient population.[9]

Better Understand the Current Clinical Trials Portfolio

Active management of the NCI portfolio is critical to identifying and prioritizing clinical research opportunities, avoiding duplicative studies, and monitoring accrual and performance of ongoing trials. The NCI Clinical Trials Reporting Program (CTRP)[10] database contains regularly updated information, including accrual, on all NCI-supported interventional clinical trials. It includes trials directly funded by NCI grants and contracts, as well as trials funded by industry and other sponsors that use the infrastructure of NCI-designated cancer centers. For dynamic areas of clinical investigation, such as immunooncology, CTRP data can help guide national efforts by enabling cancer trialists to actively identify new trials and monitor trends over time.

Future of NCI-Supported Clinical Trials

Collectively, these efforts demonstrate the ways in which NCI has continued to modernize its approach to supporting scientifically rigorous clinical trials. Tremendous opportunity and responsibility come with clinical trials. Patients participating in clinical trials must be assured that they are receiving the best possible care, that trial results will be shared with them in a timely manner, and that the trials are testing only the strongest new research concepts.

National Cancer Institute–supported clinical trials have adopted a more comprehensive, patient-centric approach that includes patients' assessments of their tolerability of therapy and quality of life, both of which directly affect prognosis, and will continue to evolve. Continued progress will require a renewed awareness that cancer is not merely "a tumor encased in a human," but rather a problem of a unique individual seeking a better outcome.

ARTICLE INFORMATION

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