

THERAPEUTICS DEVELOPMENT

A National Cancer Clinical Trials System for Targeted Therapies

John Mendelsohn

Today, modern technologies in genomics, biomarker detection, and molecular imaging are providing information that will enable physicians to select appropriate treatments for individual cancer patients from among more than 800 new experimental drugs and antibodies that target the products of the aberrant genes that can cause cancer. At this promising time in cancer research, the U.S. National Cancer Institute–sponsored collaborative clinical trials program needs an overhaul in its operations and an infusion of adequate funding. The process of clinical trial design, review for approval, and implementation must be streamlined to make it more efficient. Multiple stakeholders in the academic, governmental, and commercial sectors must better integrate their efforts. Improvements must be made in the incorporation of new technologies, prioritization, and timely completion of trials, and provision of financial support that covers actual costs. The result will be more rapid translation of recent scientific advances into increased benefits for patients with cancer.

THE PREMISE

Today, there is hope that a new era is dawning for improvement in the treatment of patients with cancer. Three lines of accomplishments are converging to enable clinical researchers to investigate therapies that target the molecular and genetic abnormalities detected in an individual patient's cancer: (i) We have identified most of the few hundred genes that are mutated or abnormally expressed in human cancers. (ii) Genome sequencing technology will soon enable us to screen the mutations in a human cancer biopsy in less than a week, at a cost of a few thousand dollars. Abnormalities in cellular proteins and RNA can already be detected in that time interval and at a reasonable cost. (iii) Pharmaceutical and biotechnology companies have more than 800 new experimental drugs and biological agents in the pipeline that are designed to target the products of abnormal genes found in human cancers (Fig. 1).

During 2010, a small number of phase I or II clinical trials have investigated experimental drugs in patients whose cancers had been shown to contain the genetic abnormality that the new drugs were designed to target. This required screening many dozens of patients in order to

identify the few who were eligible for enrollment in the trial because their cancer expressed the drug's target. The screening process paid off handsomely, with durable

response rates of greater than 50%, for example, in the recently reported phase II trial of crizotinib for the small subpopulation of lung cancer patients (~5%) with rearrangement of the *anaplastic lymphoma kinase* (*ALK*) gene. In this trial, 1500 patients seen at nine cancer centers were screened to identify 82 eligible participants (1).

The implications are tremendous for improvements in our capacity to select patients likely to respond to a new drug, to reduce the costs of clinical trials with experimental therapies, and to move more rapidly forward into registration trials for U.S. Food and Drug Administration (FDA) approval of new treatments. This hopeful scenario depends on our ability to conduct trials that screen for cancer biomarkers in tumors from a very large number of patients and investigate treatment of a selected subpopulation with a targeted experimental therapy.

The Clinical Trials Cooperative Group Program, sponsored by the National Cancer Institute (NCI), can provide the ideal mechanism for carrying out such clinical



Fig. 1. Modern medicine. Personalized information from state-of-the-art technologies in genomics, biomarker detection, and molecular imaging will permit physicians to select the appropriate treatments for individual cancer patients from the more than 800 experimental therapies that target aberrant cancer-causing gene products.

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trials (2). Over the past 55 years, this program has grown to include 10 cooperative groups, with a total of 14,000 clinical investigators from 3100 institutions and clinics, who currently enroll 25,000 patients in clinical trials each year. These publicly sponsored trials have filled an important information void by conducting head-to-head comparisons of different treatment regimens, exploring combinations of treatments, and investigating whether drugs approved for one type of cancer are effective against other types—investigations unlikely to be performed by pharmaceutical companies once a drug has received approval from the FDA for a particular indication.

The results of Cooperative Group trials have been instrumental in advancing the standard of care for cancer patients (3). Group trials were pivotal in raising the overall cure rates in children with cancer. For example, for childhood leukemia the outcome changed from a 6-month median survival to an 80% overall cure rate (3). A series of Cooperative Group trials changed the standard of treatment for breast cancer from radical mastectomy to total mastectomy, then to lumpectomy with radiation. Other trials demonstrated the benefits of adjuvant chemotherapy—additional chemotherapy treatments administered after surgical removal of a tumor—which was shown to be effective in improving 5-year survival rates and reducing deaths for patients with stage III colon cancer and stage II and III rectal cancer. Another randomized Cooperative Group trial demonstrated a 50% reduction in breast cancer incidence over a period of 5 years for high-risk, healthy women treated with tamoxifen. On the other hand, Cooperative Group research demonstrated a lack of benefit from high-dose chemotherapy with hematopoietic stem cell replacement support for the treatment of metastatic breast cancer, ending use of an aggressive therapy that entailed high rates of morbidity and mortality.

These and many dozens of other examples of Cooperative Group clinical trials that changed cancer clinical practice are presented in *A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program*, which was published in April 2010 by the Institute of Medicine of the National Academy of Sciences (4).

In this report, developed at the request

of then-NCI Director John Niederhuber, an Institute of Medicine committee identified inefficiencies and weaknesses in the current NCI-sponsored clinical trials system and made recommendations for changes on the part of the NCI and all stakeholders in cancer treatment research. The 17-member committee represented a broad range of knowledge and experience and received guidance from more than four dozen experts from the academic, government, public, and commercial sectors.

Below I summarize the committee's key findings and recommendations (4).

THE CHALLENGE

The consensus report from the committee begins with the following statement:

Clinical trials that test the safety and therapeutic benefit of drugs and other treatments are essential for developing new and improved therapies for patients with cancer. However, the system for conducting cancer clinical trials in the United States is approaching a state of crisis. Changes are urgently needed if we are to continue to make progress against the second leading cause of death in this country. If the clinical trials system does not improve its efficiency and effectiveness, the introduction of new treatments for cancer will be delayed, and patient lives will be lost unnecessarily (5).

Two statistics provide evidence of the problems that are hampering the national clinical trials process today: (i) The average time required to launch a Cooperative Group clinical trial (that is, enroll the first patient) is more than 2 years (6). Launch is preceded by many cycles of writing, reviewing, editing, modifying, and negotiating between the key stakeholders, which include clinical investigators, Cooperative Group leadership, NCI, FDA, Institutional Review Boards, and pharmaceutical companies. These same stakeholders, as well as patients with cancer, feel that this level of delay and inefficiency is unacceptable. Novel ideas become outdated. Delays add substantially to the cost of drug development. Principal investigators “burn out” and lose enthusiasm because their original innovative ideas become overly modified or no longer relevant. (ii) About 40% of NCI-supported trials that are launched do not reach their patient accrual goals and are not completed or are not published (6). These incomplete and unreported tri-

als represent a tremendous waste of effort, time, and resources and are unfair to the patients who agreed to participate. This level of noncompletion suggests that many trials are not treated as a high priority by clinical investigators or patients. Interestingly, data show that trials that require a year or less to design and launch are far more likely to reach completion (7).

Today, the opportunities for testing new targeted drugs and biologicals against cancer have never been more promising, and cancer specimens from large numbers of patients can be screened for the presence of biomarkers, which enable the selection of treatments that are more likely to be effective than those prescribed without prior genetic screening. An improved national Cooperative Group Program can provide the ideal mechanism for efficiently testing these new selective therapies. What needs to be done to make this ideal scenario a reality?

On the basis of the committee's deliberations and a review of available published literature, along with advice from experts in the field, four broad goals were proposed for enhancing the value of national Cooperative Group cancer trials, together with 12 recommendations for action supported by detailed analysis.

GOAL I

Improve the speed and efficiency of the design, launch, and conduct of clinical trials. A clinical trial is a highly complex undertaking. Analysis of the process has shown that it involves hundreds of steps, numerous decision points, and multilayered review by oversight bodies within the Cooperative Groups, government agencies, and pharmaceutical companies.

The committee's recommendations provide strategies to achieve the goal of improving efficiency and reducing the time for trial design and launch. These include some consolidation of the Cooperative Groups, disease site-specific committees, and infrastructure functions; streamlining and better coordinating the protocol development process; streamlining and harmonizing the oversight and regulation of trials by government agencies; and facilitating more effective public-private collaborations and partnerships.

Consolidation is recommended at a number of levels. The 10 Cooperative Groups could be collapsed into five or fewer. Disease site-specific committees

located within the Groups should be peer-reviewed for the quality and success of the clinical trials they have sponsored, and those with lower scores can be consolidated into the higher-ranking committees or eliminated. The result would be fewer (but more than two) disease site-specific committees of experts for each type of cancer that are charged with designing proposals for innovative clinical trials. As is currently the practice, these proposals would be forwarded to an NCI-appointed Scientific Steering Committee of experts in the particular type of cancer that decides on approval or disapproval and identifies high-priority trials. All clinical investigators in the entire Cooperative Group program should admit patients to high-priority clinical trials. The Steering Committee decisions must be respected. These changes, which represent an extension and strengthening of existing practices in the Cooperative Group program, can raise the quality of trials and lead to more rapid enrollment of patients.

The committee endorsed an earlier Operational Efficiency Working Group report, which was released just prior to the Institute of Medicine report and proposed goals for launching trials faster—phase III trials within 300 days and phase II trials within 250 days of being proposed for consideration. “Drop dead” time limits were also proposed. If the trial design process exceeds the agreed-upon metrics, it was recommended that the trial be eliminated from further consideration. To achieve these time-line targets, the committee recommended parallel rather than serial reviews by all stakeholders and improvements in all aspects of project management. Revisions should be required only if they address important questions of patient safety or scientific flaws.

The committee recommended even more aggressive consolidation of so-called back office infrastructure functions in the Cooperative Groups to reduce the current duplications in data collection and management, audit and compliance functions, credentialing of sites and clinical investigations, image storage and retrieval, drug distribution, and other procedures.

A challenging suggestion for the NCI was the recommendation that it take the lead in efforts to harmonize the oversight and regulation of cancer clinical trials by various agencies of the Department of Health and Human Services (HHS), each

of which has jurisdiction over proposed trials with different goals and criteria in mind—often leading to revisions and revisions in attempts to suit all stakeholders. In addition to the NCI, the agencies within HHS that have oversight responsibilities for cancer clinical research include a number of subunits within the FDA, the Office for Human Research Protections (OHRP), the Office for Civil Rights (OCR), and—by extension—all Institutional Review Boards. Each of these entities has a point of view that can lead to a rewrite or veto of a clinical trial protocol. The fact is there will never be a perfect clinical trial. It will never be possible to eliminate all risks and totally optimize chances for success because there will always be too many unknowns and options.

The NCI also was encouraged by the committee to continue to promote collaborations between academia, government, and the pharmaceutical industry. This is a complex endeavor that involves, for example, protection of intellectual property, frustration with prolonged time lines from many causes, and competing desires for control—each of which is discussed in the consensus report.

GOAL II

Incorporate innovative science and trial design into cancer clinical trials. The major challenge and opportunity facing the Cooperative Groups, in addition to improving efficiency and prioritization, is to take advantage of new science in the design and execution of clinical investigation. On the basis of demonstrated improvements in staging of cancers and in assessing therapeutic responses, extensive and expensive imaging studies are routinely incorporated into clinical trials today. It is clear that we will need an additional expensive step, involving the analysis of a patient's cancer for abnormalities in genes and gene products in a clinical molecular pathology laboratory. This information is becoming essential for selecting appropriate patients for clinical trials that evaluate new drugs designed to target specific genetic aberrations. However, at the present time NCI funding for such pretreatment laboratory studies is modest, and investigators must apply for such funding separately from that for performing the clinical trial. Furthermore, only modest funding is available for the equally important process of collecting and storing

tumor tissues in a standardized and fully annotated way.

The committee recommended improving the quality of and providing adequate financial support for standardized centralized biorepositories of cancer specimens from patients enrolled in clinical trials. These can be used for both prospective and retrospective analyses of biomarkers that predict the response to specific treatments as well as for prognosis.

Also recommended by the committee was continued support for developing and testing innovative designs for clinical trials that will efficiently select the most effective among many drugs against the same target and rapidly move drugs that appear effective into registration trials for FDA approval. An example is using Bayesian statistical approaches to design clinical trials that can adapt assignment of patients to trial arms on the basis of outcomes observed with prior patients in the trial (8). The I-SPY2 trial is investigating the efficacy of new drugs against breast cancer in the neoadjuvant setting (before surgery) using this adaptive approach (9).

Standardized, reproducible assessment of biomarker studies that meet Clinical Laboratory Improvement Amendments (CLIA) requirements are essential. Validation of the utility of a biomarker to identify likely responders to a new drug could be based on a positive outcome in a clinical trial testing the efficacy of that drug. Standardization is also needed for reporting the data obtained from imaging studies with computerized tomography and magnetic resonance imaging equipment in order to be able to compare trial outcomes.

Testimony from outside experts as well as specialists on the committee emphasized the need to better standardize protocols for the use of imaging equipment and to agree on standardized analytic methodologies and reporting metrics. Such standardization would permit valid comparisons of imaging data obtained at many different sites.

GOAL III

Improve prioritization, selection, support, and completion of cancer clinical trials. This goal again addresses ways of improving the efficiency of designing clinical trials and speeding up the accrual of patients to high-priority studies.

The NCI must have the major leader-

ship role in overseeing trials for which it holds the Investigational New Drug (IND) application. However, the committee recommended that when academic medical centers or companies hold the IND, the role of the NCI should be to facilitate and support high-priority trials, with less emphasis on NCI oversight. The NCI also was encouraged to oversee a more stringent peer review of Cooperative Group performance. Clinical investigators and sites with a record of poor participation in Cooperative Group trials or inadequate data management and reporting should be decertified for further participation.

Other ways of increasing the speed, volume, and diversity of patient accrual were suggested, including greater participation of patient advocacy groups in designing trials that are likely to accrue patients and in promoting subject participation. And most importantly, the costs of clinical trials must be reimbursed. Here, the data reviewed by the committee are startling. The NCI budget for Cooperative Groups research has been flat for 8 years and actually has decreased when corrected for inflation. For a physician and site participating in a clinical trial, the cost per patient to cover time, personnel, and infrastructure support is \$4700 for phase III trials and \$8450 for phase II trials, and the case payment today is only \$2000 per patient (10). Trials sponsored by industry pay far more to clinical investigators. At a time when physicians who are carrying out clinical investigations also are facing new economic challenges because of reduced reimbursements and increased costs of delivering care, the poor case reimbursement rates create a huge disincentive to participate in Cooperative Group clinical trials sponsored by the NCI.

The Groups have tried to make up reimbursement for costs by negotiating supplementary payments from pharmaceutical companies whose treatments are being tested. This type of private-public partnership should be encouraged and facilitated by the NCI—as is beginning to happen today.

At this point, it is worth considering the following questions: Who should pay for clinical research? The owner of the new therapeutic agent, who will benefit if it is successful? The NCI? Private and government payers for clinical care, as a research and development cost? The patient? This issue becomes increasingly

important at a time when the number of new targeted therapies is likely to increase tremendously. Although only a minority of new anticancer drugs introduced into clinical trials over the past few decades have been successful, better selection of appropriate patients may change this in the future. However, most trials will become more expensive as a result of the tissue biomarker analyses required. So, reluctantly, the working group reached the conclusion that if increased funding does not become available, fewer trials should be carried out. The science must be optimal, and it must be paid for.

GOAL IV

Incentivize the participation of patients and physicians in clinical trials. The final goal addressed by the committee focused on the needs of patients and their physicians and whether they are incentivized to participate in clinical trials.

More and more patients understand that at some point in the course of their disease, a clinical trial may be their best treatment option—better than what is considered standard practice. Having overcome the reservations about “being an experiment,” a remaining concern for these patients is the cost of therapy. Medicare policy supports the requirements to pay for the non-study-related costs of care in clinical trials, but Medicare subcontractors vary in their interpretation of the policy. Half of the states also require medical insurance companies to pay for patient-care costs not related to the experiment. However, the Federal Employees Health Benefits Program and Employee Retirement Income Security Act (ERISA)–governed plans, which cover the medical care of a major proportion of Americans, do not have similar rules. The new Patient Protection and Affordable Care Act signed into law by U.S. President Barack Obama in 2010 (11) will require these payments if the intent of the law is converted into enforced policy. This advance would greatly aid in incentivizing patient participation in clinical trials.

Other suggestions include a new medical current procedural terminology (CPT) billing code, with higher payments for care administered in the context of a clinical trial that is vetted by peer review. This change would have to be proposed by the American Medical Association.

Of course, motivated physician-

investigators who commit the extra time required to design a clinical trial or to enroll and follow patients in a trial are critical for the advancement of cancer treatment. In addition to the lack of appropriate payment for physician effort in performing NCI-sponsored Cooperative Group clinical trials, there is another impediment to participation by most physicians who are on academic faculties. Most of our academic medical centers do not reward excellence, skill, and peer recognition in clinical trials research at a level comparable with that for faculty engaged in laboratory research. Laboratory investigation usually trumps clinical science when tenure, promotion, faculty start-up funding, and protected time are under consideration by deans and faculty committees. The committee advised that academic medical centers accelerate the trend to develop metrics for assessing clinical and team-based research and policies that recognize, incentivize, and reward these investigators and then to use these policies and metrics in decisions relating to resource allocation, promotion, and tenure.

The committee recognized that there are many stakeholders in the clinical trials process, each of which sees the challenges through a different pair of lenses. It concluded that:

Collectively, the implementation of these recommendations would reinvigorate the Clinical Trials Cooperative Group Program for the 21st century and strengthen its position as a critical component of the translational pathway from scientific discovery to improved treatment outcomes for patients with cancer. Modifying any particular element of the Program or the clinical trials process will not suffice; changes across the board are urgently needed. All participants and stakeholders ... must reevaluate their current roles and responsibilities in cancer clinical trials and work together to develop a more effective and efficient multidisciplinary trials system (12).

Although plagued by difficult problems, the Cooperative Group program faces challenges that are not intractable. The ultimate goal is for stakeholders to retain current strengths and to reorganize structures and operations so as to create a more effective national clinical trials network. Such a network would perform efficient, biomarker-driven trials with modern can-

cer therapies that enhance and personalize patient care and reimburse physicians for the full cost of their participation.

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