Clinical Trials: The Crux of Cancer Innovation

Even as medical science is transforming cancer care, major deficiencies in the way cancer clinical trials are designed, carried out, regulated and funded in the United States are impeding the pace of discovery. According to reports from the Institute of Medicine (IOM) and the President's Cancer Panel, as well as the observations of numerous stakeholders – including the National Cancer Institute, clinical investigators, patient advocates and industry sponsors, the current clinical trial system can be improved in order to expedite patient access to safe and effective breakthrough treatments.

Now, a new white paper, *Securing the Future of Innovation in Cancer Treatment*, adds to this assessment, pointing to logistical, institutional, regulatory and enrollment hurdles that are driving up the costs and delaying the development of new treatments – factors that may ultimately harm patients. The paper, written by the National Patient Advocate Foundation in collaboration with other stakeholders, highlights key factors of the current state of cancer clinical trials and new models for improving speed and efficiency.

The Role of Cancer Clinical Trials

Clinical trials are essential in translating new knowledge into tangible benefits for patients and making it possible for enrolled patients to receive promising new interventions that may extend their lives. These studies take place at cancer centers and other medical institutions, community hospitals and clinics, veterans' and military hospitals, and doctors' offices across the U.S. and in other countries. They entail four different phases of clinical research, as follows:

- ***Phase 1 Trials*** – usually enrolling a small number of volunteers, these are the first studies done with people to evaluate how a new drug should be given (by mouth, injected into a vein, or injected into the muscle), how often, and what dose is safe.

- ***Phase 2 Trials***–these studies test the safety of the experimental drug in about 100 to 500 patients, examine the possible short-term side effects and risks associated with the drug and begin to evaluate how well the new drug works against a particular kind of cancer.

- ***Phase 3 Trials*** – in these studies, the new drug, vaccine or a new combination of drugs is tested in about 1,000 to 5,000 patients compared to a placebo or the current standard treatment, with the goal of generating statistically significant data about safety, efficacy and the overall benefit-risk relationship of the experimental therapy. In most instances, phase 3 studies are placebo-controlled, randomized and double-blinded. Accordingly, each of the study subjects is assigned randomly to one of the treatments and neither the researchers nor the subjects know which treatment is being delivered until the study is over.

- ***Phase 4 Trials*** – often referred to as post-marketing surveillance trials, these studies often involve several thousand people and are used to further evaluate the effectiveness and long-term safety of a new drug /vaccine after the new therapy has been approved by the Food and Drug Administration (FDA) and is on the market. In some cases, FDA requires phase 4 studies to assess how a new medicine affects a specific subgroup of patients.

To ensure these studies meet their specific goals and requirements while protecting the safety and rights of participants, cancer clinical trials are regulated by the FDA and overseen by an Institutional Review Board (IRB), which approves the research design and protocol, requires modifications as necessary, and maintains oversight of the study. In addition, some trials, and especially Phase 3 studies, use a Data and Safety Monitoring Board (DSMB) to monitor the safety and progress of the trials. Similar to IRBs, DSMBs review the progress of a clinical trial and participant safety. They also review data on the effectiveness of the trial interventions and can stop a trial early if safety concerns arise or if an answer to the main research question is obtained earlier than expected.

With these many phases and procedures involved, the clinical trial process has always been lengthy and costly. However, as the environment has become increasing complex, added steps and inefficiencies have increased the time and costs considerably. One report found it takes an average of 2.5 years to open a Phase 3 clinical trial sponsored through the National Cancer Institute's Clinical Trials Cooperative Group Program, with some studies taking more than four years to activate. Accordingly, streamlining the clinical trials process and eliminating logistical obstacles will go a long way in expediting the development of innovative cancer therapies.

Factors Impeding Innovation and Patient Participation

Clinical trials are essential to the advancement of cancer care, but delays in access to new therapeutic innovations and administrative burdens that discourage physician and patient participation in cancer research studies impede optimal care. Today, only 30 percent of clinical trial enrollment is domestic, and the number of physicians participating in clinical research has dropped. Consequently, few cancer patients are able to locate and enroll in clinical trials.

Contributing to this situation are number of inter-related factors that affect every stage of the clinical trials process and all stakeholders – from the scientists who design and conduct the studies to the patients who take part in these trials. The following describes these factors and the challenges they represent.

Patient-Related Factors

The accrual of adequate numbers of people to participate in medical research studies is an ongoing problem for biomedical researchers. Today only 2-5 percentof the more than 13 million adults with cancer in the U.S. population participate in cancer clinical trials. In addition, the patient population most affected by cancer, older adults, is often excluded or under-represented in studies on new cancer therapies. While 77 percent of cancers in the United States are diagnosed in people 55 and older,studies find that only 25 percent of the participants in national clinical trials are over 65 years of age.

There are numerous barriers contributing to this lack of patient participation, including misperceptions about clinical trials, lack of awareness of trial availability, fear of adverse effects, the complexity of consent forms and other materials for patients, as well as practical issues, such as transportation to and from the trial site and being able to take time off from work. Research also finds that income is a precluding factor for many cancer patients. One recent study reported that cancer patients who made less than $50,000 a year were 30 percent less likely to participate in a clinical trial than those with a higher income.

Concerns about Insurance Coverage

Although trial sponsors are required to cover the cost of tests, procedures, drugs, extra doctor visits and any research directly related to the study itself, a major barrier to patient accrual involves reimbursement for routine patient care costs. These costs include the charges that insurance would normally be expected to cover, such as physician fees, hospital charges, and routine tests. However, because of concerns about liability for the added costs of research-related complications, many insurance companies provide no coverage for these services when they are administered as part of the clinical trial process. In this situation, patients are often left with a choice between paying out of pocket for the clinical trial and forgoing the trial altogether. Of particular concern is coverage of clinical trials for children, especially those suffering from cancer.

To remedy this situation, some states require health plans to cover the routine costs of clinical trials, and provisions of the Affordable Care Act (ACA) have gone into effect which set a national minimum coverage standard and new requirements for coverage in all 50 states and the District of Columbia. In addition, the Medicare program covers the routine patient costs for "qualifying" clinical trials, that is, those that have a therapeutic benefit. While these developments are certainly good news for patients and researchers, questions remain about what costs are actually covered. This is especially the case with the new ACA provisions, for which regulations have yet to be developed, so payers are expected to adhere to this provision in good faith.

Physician-Related Factors

For many patients, one of the biggest stumbling blocks to taking part in a medical research study is the advice of their doctor. However, numerous assessments document the many challenges practitioners face when referring patients, including the time to counsel and refer patients, increased paperwork and record-keeping requirements, and financial disincentives. According to a survey of oncologists commissioned by the American Society of Clinical Oncologists (ASCO), the cost to physicians for data management and other research expenses associated with enrolling a patient in a Phase 3 trial is approximately $2,000.

Besides referring patients, oncologists also conduct clinical research. A 2013 ASCO member survey finds that declining federal funding for clinical trials coupled with the rising costs of increasingly complex studies is having a direct impact on physicians' ability to conduct cancer research. Seventy-five percent of survey respondents said their research budgets were decreased, forcing many physicians to delay clinical trials or restrict the research questions or clinical trial endpoints to reduce study costs.

Logistical and Regulatory Obstacles

By their nature, clinical trials are a thorough, resource-intensive process of scientific evaluation. Thus, time, money, personnel, medical supplies, support systems and a clear plan for completing the necessary steps in a trial are all part of the clinical research infrastructure. Among the many hurdles are duplicative and competing standards, competing IRB requirements for consent forms and protocols, documentation and auditing mandates, increasing regulatory requirements and delays in review decisions.

Clinical trials can be conducted relatively easier overseas, where sponsors are able to enroll tens of thousands of patients quickly and save substantial development costs. According to a recent study, one-third of Phase 3 trials for the 20 largest U.S. pharmaceutical companies are being conducted solely outside the U.S. In addition, the study also found that academic sponsors are also looking to conduct

trials internationally.

Accelerating Progress

Through Innovative Model Programs
Because clinical trials are essential to transform cancer care, the NPAF white paper calls for collective action to improve the ways in which oncology trials are funded, designed, implemented and regulated in the U.S., building on some innovative models that can be replicated.

Regarding new funding models for clinical trials, an innovative strategy is the Clinical Accelerator program developed by the non-profit Clinical Research Institute (CRI) , which allows investors to provide capital to promising clinical trials in exchange for the potential of future earnings if the drug is approved and commercialized. CRI also operates the Cancer Research Institute's Venture Fund, which gives small biotech companies access to the organization's proprietary reagents and cancer immunotherapy clinical trials network in exchange for access to their reagents for testing in combination clinical trials.

Looking to new ideas for designing next-generation cancer clinical trials, another model is the "bring the protocol to patients" or P2P clinical trials concept. Through this method, drug sponsors are able to move through clinical testing much faster by recruiting patients with different cancers to receive investigational targeted drugs selected to match the distinct genetic changes found in each patient's tumor. Novartis' Simplified Institutional Review Board Process, called "SIGNATURE," is one example. Through this new protocol, cancer patients are tested for the presence of the relevant changes in their tumor. Once the testing results are verified, the IRB rules on the eligibility of the patient to be treated with an investigational therapy based on the molecular blueprint of the tumor. At the point, patients start treatment in one of the clinics signed up to participate in the trial. This new approach to clinical trial design speeds up the process and allows sponsors to test a promising agent against genetic abnormalities that may be common to multiple cancer types.

Also worthy of attention is a new initiative to address costly inefficiencies in clinical trials. Called TransCelerate BioPharma Inc. ("TransCelerate"), this non-profit consortium of 18 biopharmaceutical companies was formed in 2012 to streamline the clinical trial system by creating common clinical trial protocol templates, developing clinical trial networks, and establishing a global investigator registry. Among its initiatives, TransCelerate published a position paper outlining a methodology for risk-based site monitoring ("Risk-Based Monitoring" or "RBM") that could significantly modernize and streamline the way studies are conducted and monitored.The consortium also created minimum criteria for Good Clinical Practice (GCP) training to end the redundant GCP training programs and collection of non-study specific information that require investigators to complete multiple questionnaires and forms and take duplicative training courses before starting each trial.

Achieving Success through Three Pillars of Innovation
Building on these successes, the NPAF paper identifies some readily achievable solutions to improve cancer clinical trials and accelerate biomedical discovery. The result is a blueprint for action that involves three pillars of innovation:

1. **Expand the science of innovation by reducing regulatory and logistical obstacles.**
   This will require moving to a more standardized regulatory-approval process; expanded use of

smaller, more targeted clinical trials and adaptive protocols to study specific subsets of patients; expedited patient access to innovative new therapies before they are approved for general use, and creation of a centralized, nationwide hub from which data relating to cancer trials can be accessed and shared.

2. **Improve the value of innovation by bolstering funding opportunities.**
   Building on the Cancer Research Clinical Accelerator program, NPAF encourages a new wave of experimentation in research funding and incentives that encourage more venture capital in cancer research. It is also imperative that all stakeholders align around the need for increased congressional appropriations for government-funded cancer research, especially for basic biomedical research, a key driver of late-stage research.

3. **Enhance the delivery of innovation through improved communication and coordination between providers and patients.**
   Increased patient participation in cancer clinical trials requires improved communication and coordination between providers and patients. One critical priority is to improve the informed consent process so consent forms are in plain language and there is a discussion with the patient about the consent form and clinical trial process. Patients also need easy to understand information about patient clinical trial costs that will be covered under the Affordable Care Act and the Medicare Program.

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